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Review

The hallmarks of cancer immune evasion

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SUMMARY

According to the widely accepted "three Es" model, the host immune system eliminates malignant cell precursors and contains microscopic neoplasms in a dynamic equilibrium, preventing cancer outgrowth until neoplastic cells acquire genetic or epigenetic alterations that enable immune escape. This immunoevasive phenotype originates from various mechanisms that can be classified under a novel "three Cs" conceptual framework: (1) camouflage, which hides cancer cells from immune recognition, (2) coercion, which directly or indirectly interferes with immune effector cells, and (3) cytoprotection, which shields malignant cells from immune cytotoxicity. Blocking the ability of neoplastic cells to evade the host immune system is crucial for increasing the efficacy of modern immunotherapy and conventional therapeutic strategies that ultimately activate anticancer immunosurveillance. Here, we review key hallmarks of cancer immune evasion under the "three Cs" framework and discuss promising strategies targeting such immunoevasive mechanisms.

INTRODUCTION

Contrary to the outdated view of cancer as an immune agnostic disease, malignant cell precursors can be efficiently eliminated by the immune system.[1,2] Natural killer (NK) cells, which are activated by rather non-specific signals of distress exposed on the surface of cells experiencing perturbations of homeostasis, play a critical role in the elimination of recently transformed cells.[3,4] In some cases however, malignant cell precursors can form microscopic neoplasms that display accelerated proliferation, but such lesions exist in a dynamic equilibrium with the host immune system, which prevents outgrowth and hence both local and metastatic dissemination.[1,2] $CD8^+$ cytotoxic T lymphocytes (CTLs), which are activated by antigenic determinants presented on the surface of malignant cells in complex with major histocompatibility complex (MHC) class I molecules, are essential to confine the growth of microscopic tumors,[5,6] but at the same time they edit them through Darwinian mechanisms, ultimately favoring the selection of cancer cell clones with genetic or epigenetic alterations that enable overt immuno escape.[7,8]

According to this conceptual framework, which is commonly referred to as the "three Es" model, progressing neoplasms become clinically manifest only when malignant cells develop the ability to evade immune recognition and elimination,[2] a process that—similar to the pathogen-host co-evolution—involves the acquisition of specific features by malignant cells under the selective pressure of the host immune system.[9] Importantly, malignant cells can acquire overtly immunoevasive properties by a number of different mechanisms, which is fundamental not only for them to form locally invasive and metastatic lesions, but also for established tumors to resist therapeutic challenges and relapse.[10,11] While this may seem trivial for modern immunotherapy, which purposely aims at (re)activating tumor-targeting immunity,[1] immunoevasion also contributes to the resistance of some tumors to treatments that mediate clinically relevant immunostimulatory effects even though they have been developed in an immune agnostic manner, including some chemotherapeutics,[12] targeted anticancer agents,[13] and (at least in some settings) radiotherapy.[14] In line with this notion, considerable efforts are being dedicated to the development of clinically viable strategies that prevent or reverse immunoevasion to be employed either as standalone therapeutic approaches or in combination with established treatments.[15–17]

Inspired by the "three Es" model, we propose that the mechanisms through which cancer cells evade tumor-targeting immunity can be interpreted under a "three Cs" conceptual framework involving camouflage, coercion, and cytoprotection, which refer to the ability of some malignant cells to evade recognition by the immune system (i.e., not be found by immune effector cells or not be identified as malignant), directly or indirectly interfere with immune effector cells (i.e., once found by immune effector cells and identified as malignant, prevent immune cell activation), and protect themselves from immune cytotoxicity (i.e., resist effector molecules normally released upon immune cell activation),

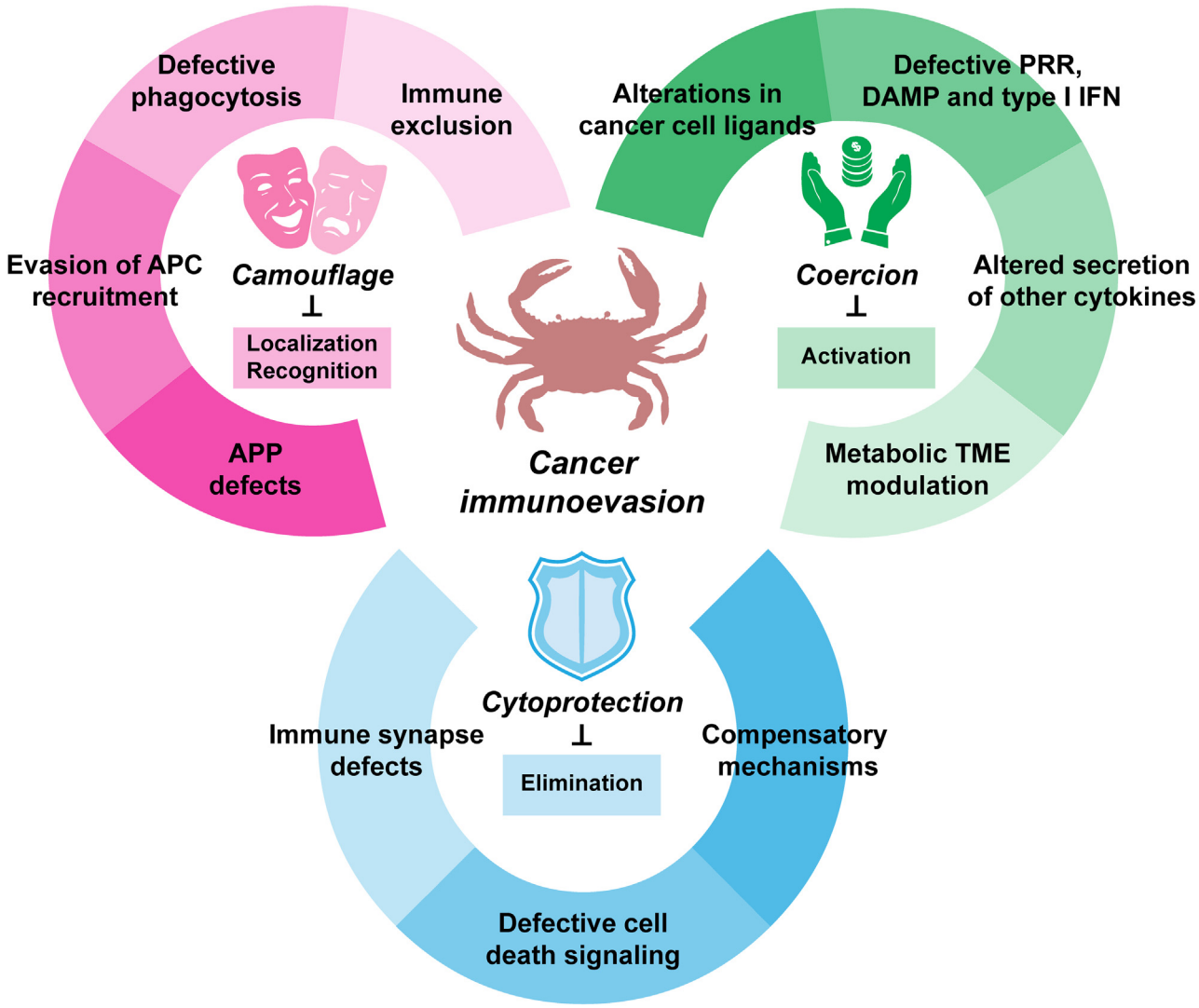

Figure 1. The "three Cs" of cancer immune evasion

Malignant cells can evade immune surveillance by (1) avoiding being localized by immune effector cells or being recognized as neoplastic (camouflage), (2) preventing immune cell activation despite being localized and recognized as neoplastic (coercion), or (3) protecting themselves from immune cytotoxicity in the context of normal immune cell activation (cytoprotection). APC, antigen-presenting cell; APP, antigen processing and presentation; DAMP, damage-associated molecular pattern; IFN, interferon; PRR, pattern recognition receptor; TME, tumor microenvironment.

respectively (Figure 1). In addition to reviewing these hallmarks of cancer immunoevasion under the "three Cs" paradigm, here, we discuss promising strategies to prevent or reverse such immunoevasive mechanisms for therapeutic purposes. Importantly, host alterations related to these hallmarks, including (1) polymorphisms in genes encoding key receptors, (2) immunological alterations of the tumor microenvironment (TME) driven by non-malignant cells, (3) defects in the whole-body ecosystem that are not elicited by neoplastic cells, go beyond the scope of the present review and hence will not be discussed.

CAMOUFLAGE

One major strategy for malignant cells to evade immunosurveillance relies on their ability to hide from immune effector cells, i.e., to avoid being localized by immune effector cells or being recognized as transformed. Such a camouflage can results from defects in antigen processing and presentation, from the limited secretion of chemotactic factors associated or not with immunogenic cell death (ICD), or from the creation of stromal barriers preventing immune infiltration (Figure 2).

Antigen processing and presentation defects

Both mutational and non-mutational events provide cancer cells with a distinct antigenic landscape compared to their normal counterparts, at least theoretically increasing their visibility $CD8^+$ CTLs.[18,19] However, the molecular machinery underlying the proper processing and exposure of such neoantigens on the cell surface is often defective in malignant cells, allowing them to avoid immune recognition.[18] Supporting the clinical

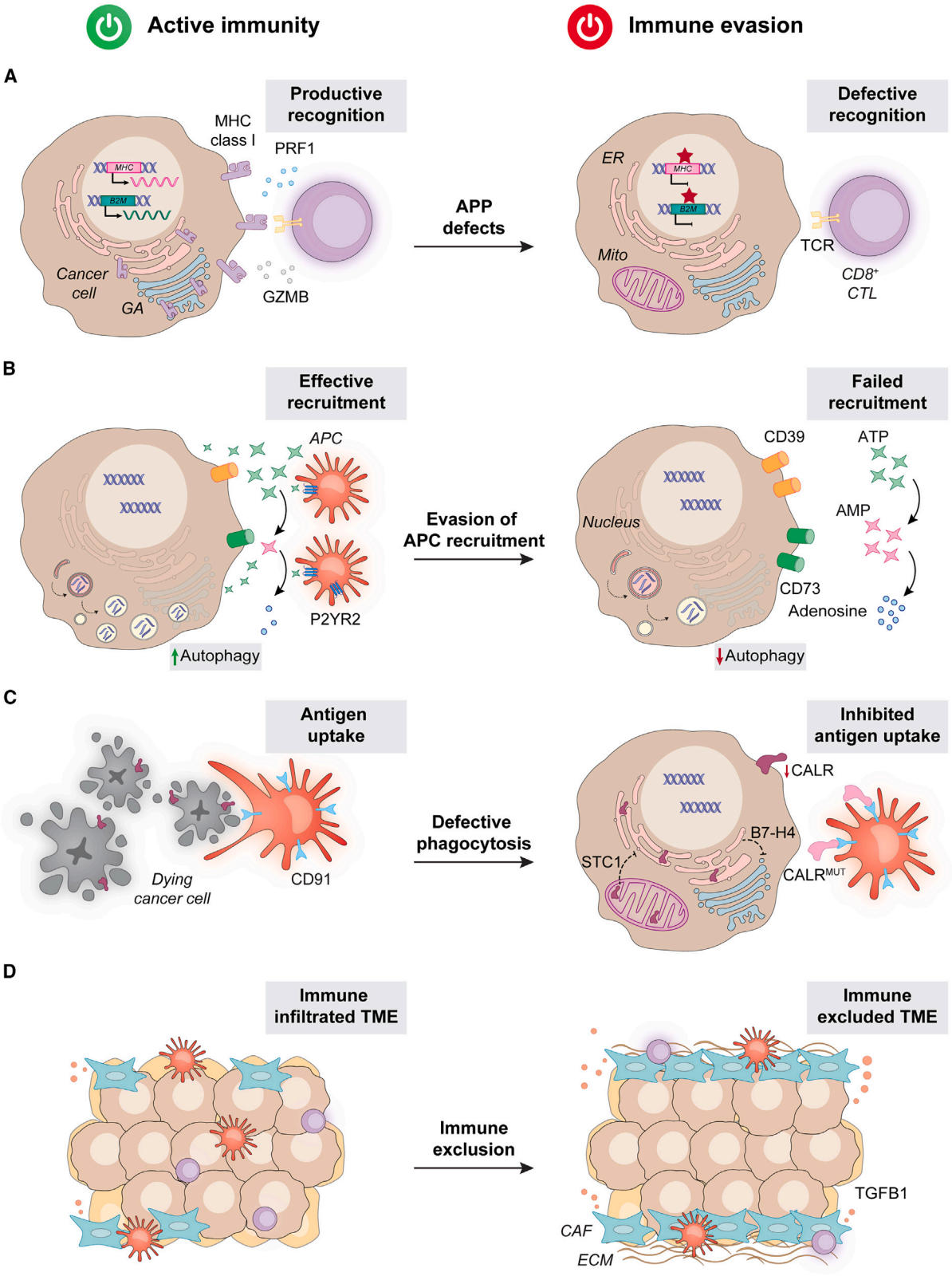

Figure 2. Camouflage in cancer immune evasion

Neoplastic cells can avert tumor-targeting immunity through multiple alterations that ultimately prevent them from being detected or contacted by immune effector cells. These include (but may not be limited to) (1) defects in the antigen and presentation (APP) machinery, as exemplified by mutations in genes

(legend continued on next page)

relevance of such a camouflage strategy, a reduced mutational or neoantigen burden has been correlated with inferior disease outcome in various cohorts of patients with cancer receiving immune checkpoint inhibitor (ICI)-based immunotherapy.[20–23]

Neoplastic cells can acquire defects in the antigen processing and presentation (APP) machinery via genetic mechanisms, including mutations in genes encoding MHC molecules or the obligate MHC class I interactor beta-2 microglobulin (B2M) as observed across a variety of tumors,[24] as well as loss of heterozygosity (LOH) at chromosome 6p, which encompasses the MHC locus, as documented in patients with non-small cell lung carcinoma (NSCLC) and homologous recombination-deficient (HRD) high-grade serous ovarian cancer (HGSOC).[25–27] Moreover, defective antigen presentation in malignant cells can emerge from epigenetic mechanisms. This can occur via the accumulation of repressive histone acetylation marks as consequent downregulation of APP component including proteasome 20S subunit beta 8 (PSMB8, best known as LMP7), PSMB9 (best known as LMP2), transporter associated with antigen processing 1 (TAP1), and TAP2, which is frequent in Merkel cell carcinoma (MCC),[28] as well as through the establishment of repressive histone 3 trimethylation marks (namely H3K9me3 and H3K27me3) at the promoter region of MHC-encoding genes, an immunoevasive mechanism that is common in hematological malignancies and is initiated by enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) and SET domain bifurcated histone lysine methyltransferase 1 (SETDB1).[29,30] A similar epigenetic camouflage has also been observed in other solid tumors.[31–34] Of note, immunoevasive malignancies often exhibit reduced DNA methylation in specific genomic regions that promote the formation of transcriptional inactive heterochromatic structures known as partial methylation domains (PMDs). Such PMDs have been associated with the silencing of various immunomodulatory genes, including APP-related genes.[35]

Additional examples of epigenetic camouflage have been reported in advanced prostate cancer, a setting in which downregulation of melanocyte inducing transcription factor (MITF) results in MHC class I silencing upon expression of eukaryotic translation initiation factor 3 subunit B (EIF3B),[36] as well as in melanoma, which can limit MHC class I expression upon transactivating the embryonic transcription factor double homeobox 4 (DUX4).[37] Moreover, the epigenetic repression of APP is frequent among cancer stem cells (CSCs), a small population of malignant cells with superior tumor-repopulating potential that can self-renew while generating a more differentiated progeny.[38] While some of these mechanisms are *de facto* shared with normal stem cells from the hair follicle and muscle, suggesting that the normal stem cell compartment also benefits from immunoevasion,[39] others appear to be specific for CSCs, and hence potentially relevant for therapeutic purposes. As a standalone example, melanoma- and breast cancer-initiating cells have been shown to repress APP-relevant genes upon the epigenetic upregulation of the RNA-binding protein cold shock domain-containing protein E1 (CSDE1) and consequent inactivating dephosphorylation of signal transducer and activator of transcription 1 (STAT1) (see in the following text).[40]

Of note, post-translational mechanisms have also been shown to cause APP defects in cancer cells. Specifically, NBR1 autophagy cargo receptor (NBR1) has been shown to cause the degradation of MHC class I molecules via autophagy (a catabolic pathways that is generally upregulated in cancer cells),[41] at least in pancreatic malignancies.[42,43] Similarly, proprotein convertase subtilisin/kexin type 9 (PCSK9), a key regulator of cholesterol metabolism, reportedly inhibits MHC class I molecule expression by favoring their lysosomal degradation via a cholesterol-independent mechanism.[44] Moreover, acute myeloid leukemia (AML) cells appear to degrade MHC class I molecules via the ubiquitin-proteasome system, through a mechanism that depends on sushi domain containing 6 (SUSD6), transmembrane protein 127 (TMEM127), and WW domain containing E3 ubiquitin protein ligase 2 (WWP2).[45]

Corroborating the importance of APP-related camouflage for immune evasion, the downregulation of MHC class I molecules is a common mechanism of acquired resistance to immunotherapy. For instance, late relapse in patients with metastatic MCC treated with adoptive cell therapy (ACT) plus ICI-based immunotherapy has been associated with the transcriptional repression of MHC genes presenting the ACT target.[46] Along similar lines, early treatment biopsies from melanoma patients refractory to ICIs have revealed an enrichment of malignant cells characterized by transcriptional reprogramming toward a mesenchymal-like state with suppressed APP that depended on transcription factor 4 (TCF4).[47]

Another camouflage strategy harnessed by cancer cells involves the genetic or epigenetic downregulation of dominant neoantigens driving immune recognition.[18] While this is particularly frequent when one or a few antigens drive anticancer immunity, such as in patients with hematological malignancies receiving chimeric antigen receptor (CAR) T cells,[48] it has also documented in patients with melanoma undergoing ICI-based immunotherapy,[49,50] as well as in patients with treatment-naïve NSCLC, a setting in which neoantigen-expressing genes appeared to be silenced upon promoter hypermethylation.[25] A similar mechanism has been recapitulated in a syngeneic mouse model of melanoma receiving ACT.[51] In this latter setting, epigenetic modifiers such as azacitidine and decitabine partially restored neoantigen expression and immunological disease control.[51]

Collectively, these observations suggest that genetic and epigenetic mechanisms affecting APP are a major source of

encoding MHC molecules or the obligate MHC class I interactor beta-2 microglobulin (*B2M*), which prevents the recognition of malignant cells by $CD8^+$ cytotoxic T lymphocytes (CTLs) (A); (2) a defective recruitment of antigen-presenting cells (APCs) or the precursors thereof to the tumor bed, as exemplified by the upregulation of enzymes that convert extracellular ATP into adenosine, such as ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD1, best known as CD39), ectonucleotidase 5′-nucleotidase ecto (5NTE, best known as CD73) as well as the downregulation of autophagy (B); (3) defects in the engagement of phagocytosis by APCs, as exemplified by a variety of mechanisms preventing the immunogenic cell death (ICD)-associated exposure of the endoplasmic reticulum (ER) chaperone calreticulin (CALR) on the cell surface (C); and (4) the physical exclusion of immune effector cells from cancer cell nests, as exemplified by the cancer-associated fibroblast (CAF)-driven and transforming growth factor β 1 (TGFB1)-dependent establishment of a dense, collagen-rich stromal reaction (D). B7-H4 (official name: (VTCN1), V-set domain containing T cell activation inhibitor 1; CD91 (official name: LRP1), LDL receptor-related protein 1; ECM, extracellular matrix; GA, Golgi apparatus; GZMB, granzyme B; P2RY2; purinergic receptor P2Y2; PRF1, perforin 1; STC1, stanniocalcin 1; TCR, T cell receptor.

camouflage for cancer cells. Importantly, these defects can emerge both in the context of natural immunoevasion (and hence be potential sources of innate resistance to immunotherapy) or as a result of a selective pressure imposed by immunotherapy (acquired resistance). Of note, APP is upregulated by both type I interferon (IFN) and interferon gamma (IFNG) signaling.[52] However, given the broader impact these factors have on the TME, we will discuss them as part of coercion (see in the following text). Along similar lines, considerable defects in APP as those elicited by *B2M* loss are expected to generate a potent activatory signal for NK cells,[53] which requires the acquisition of coercive mechanisms based on NK cell-inhibitory ligands (NKILs, also discussed in the following sections).

Evasion of APC recruitment

Malignant cells can succumb to various therapeutic agents via a variant of cell death that is sufficient to elicit antigen-specific immune responses associated with an effector phase and immunological memory, i.e., ICD.[54] ICD relies on the pre-mortem activation of stress response pathways including (but not limited to) autophagy and the integrated stress response (ISR)—a cellular mechanism of protection from endoplasmic reticulum stress[55]—that culminate with the production of chemotactic, pro-phagocytic, and immunostimulatory signals for antigen-presenting cells (APCs) or the precursors thereof that are cumulatively referred to as damage-associated molecular patterns (DAMPs).[54] Of note, while both preclinical and clinical data suggest that multiple malignancies benefit from defects in the molecular machinery underlying ICD-associated DAMP emission, fully harnessing ICD induction as a means to increase ICI sensitivity in clinical settings remains challenging.[14,54] Whereas defects in ICD-related immunostimulation are a source of coercion (see in the following text), the lack of interaction between cancer cells and APCs as promoted by defective chemoattraction or exposure of pro-phagocytic signals constitutes a common mechanism of camouflage.

Defective release of chemoattractants

Malignant cells undergoing ICD release ATP and ANXA1, which operate as mid-range and short-range chemoattractants for APCs upon binding to purinergic receptor P2Y2 (P2RY2) and formyl peptide receptor 1 (FPR1), respectively.[56–58] Corroborating the importance of these signals for the initiation of anticancer immunity, cancer cells generally acquire several mechanisms to suppress ICD-related ATP and ANXA1 release.

Specifically, multiple cancer cells appear to express increased levels of ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD1, best known as CD39) and/or 5′-nucleotidase ecto (NT5E, best known as CD73), which sequentially convert extracellular ATP into ADP, AMP and the potent immunosuppressive metabolite adenosine.[59] In line with this notion, CD39 overexpression as well as the pharmacological or genetic blockage of purinergic receptors has been shown to abolish APC recruitment and ICD-driven antitumor immunity as induced by administration of ICD-inducing anthracyclines in syngeneic mouse models of fibrosarcoma.[60] Similar results have been obtained by the genetic inactivation of autophagy in malignant cells, knowing that optimal autophagic responses to stress ensure proper ATP secretion during ICD.[61] Conversely, pharmacological or nutritional whole-body hyperactivation of autophagy has been shown to boost the efficacy of ICD-inducing therapeutic regimens in a variety of syngenetic tumor models.[62,63] In line with these observations, the expression of the autophagic marker microtubule-associated protein 1 light chain 3 beta (MAP1LC3B, best known as LC3B) has been positively correlated with abundant immune infiltration and improved disease outcome in patients with breast carcinoma.[64] Similar to defects in ATP release, the deletion of *Anxa1* from mouse fibrosarcomas, colorectal cancers (CRCs) and mammary cancers compromises their ability to respond to immunogenic chemotherapy *in vivo*.[58,65] Moreover, higher-than-median levels of ANXA1 have been associated with an improved recruitment of APCs and T cells in patients with CRC, NSCLC as well as breast and kidney cancer.[66]

ICD is also associated with the release of chemokines that recruit immune effector cells to the TME, notably C-X-C motif chemokine ligand 10 (CXCL10) and (at least n some settings) C-C motif chemokine ligand 2 (CCL2).[54] Defects in CXCL10 release downstream of failed type I IFN signaling in cancer cells succumbing to ICD induction by anthracyclines have been mechanistically linked to decreased disease control in syngeneic mouse models of fibrosarcoma.[67] Along similar lines, both *CXCL10* and *CXCL9* are transcriptionally repressed by epigenetic modifiers such as EZH2 and DNA methyltransferase 1 (DNMT1) in ovarian cancer, resulting in poor recruitment of effector T cells to the tumor site.[68] Decreased CXCL10 secretion also appears to promote camouflage and immunoevasion in melanomas with elevated glycolytic activity.[69] Finally, genetic defects in ICD-associated CCL2 release or sensing have been associated with reduced APC recruitment and compromised anticancer immunity in preclinical models of fibrosarcoma.[70] That said, CCL2 also appears to mediate robust coercive effects (see in the following text).

Activation of the ISR by a low-protein diet reportedly elicits therapeutically relevant tumor-targeting immune responses in immunocompetent mice bearing CT26 CRCs via a mechanism that (at least in part) involves CXCL10-dependent chemoattraction.[71] Similar results have been obtained by genetically activating the ISR via ADP ribosylation factor 1 (*Arf1*) deletion in preclinical models of CRC.[72] Moreover, signs of ISR activation in malignant cells, notably the pathognomonic activating phosphorylation of eukaryotic translation initiation factor 2 subunit alpha (EIF2S1, best known as eIF2α), have been correlated with improved disease outcome in various cohorts of patients with cancer.[73] However, it is likely that such an advantage may also relate to the critical role of the ISR in exposure of calreticulin (CALR), an ER chaperone with pro-phagocytic activity once translocated to the outer leaflet of the plasma membrane (see in the following text).[74] Activation of the ISR (or at least modules thereof) has also been associated with detrimental cancer cell phenotypes including (1) the inhibition of antigen presentation on MHC class I molecules downstream of mitochondrial fragmentation[75]; (2) the outgrowth of disseminated cancer cells despite MHC class I expression; (3) the survival of glioblastoma (GBM) CSCs exposed to adverse microenvironmental conditions[76]; as well as (4) the generation of drug-tolerant colorectal and lung cancer cells.[77] Whether the immune system is involved in these latter two phenotypes, however, remains to be elucidated.

Of note, the release of ICD-unrelated chemoattractants can also be defective in some tumors, which also represents a

camouflage mechanism. For instance, histone deacetylase 8 (HDAC8) reportedly promotes the transcriptional repression of CCL4, a potent T cell chemoattractant, in models of hepatocellular carcinoma (HCC), *de facto* limiting anticancer immunity.[78] Along similar lines, in breast, colorectal, and lung cancer, defects in the secretion of CCL20 hamper the recruitment $CCR6^+$ type 3 innate lymphoid cells (ILC3s) to the tumor site, resulting in decreased tumor infiltration by $CD4^+$ and $CD8^+$ T cells and limited responsiveness to ICIs.[79]

In summary, defects in chemoattraction promote camouflage in variety of cancer types, resulting in limited tumor infiltration by immune effector cells and hence poor disease outcome.

Defective ICD-driven phagocytosis

The ICD-associated exposure of CALR on the surface of cancer cells, which mechanistically impinges on the ISR and eIF2α phosphorylation, provides a potent pro-phagocytic signal to APC upon binding to LDL receptor-related protein 1 (LRP1, also known as CD91).[74] Besides explaining at least some facets of camouflage as emerging in the context of suboptimal ISRs (see mentioned previously), this accounts for multiple instances of camouflage related to suppressed phagocytosis. Malignant cells have indeed been shown to avoid CALR-mediated phagocytosis by APCs by: (1) downregulating CALR expression, which reportedly has negative prognostic value in hematological malignancies like AML,[80,81] as well as in some solid tumors including NSCLC[82]; (2) trapping CALR at mitochondria upon overexpression of stanniocalcin 1 (STC1), which is common across cancer types[83]; (3) upregulating V-set domain containing T cell activation inhibitor 1 (VTCN1, best known as B7-H4), which, besides being a potent co-inhibitory ligand for T cells (see in the following text), also inhibits eIF2α phosphorylation[84]; and (4) secreting a truncated forms of CALR, competitively inhibiting the interaction between surface-exposed CALR and CD91.[85]

In line with these observations, pharmacological and genetic strategies that block CALR exposure on cancer cells experiencing immunogenic stress and death have been linked to immunoevasion in a variety of syngeneic tumor models.[86–89] Conversely, improving the (otherwise suboptimal) externalization of CALR has been associated with improved immunogenicity in preclinical models of fibrosarcoma and multiple myeloma.[90,91] Of note, defects in CALR exposure also endow cancer cells with the ability to inhibit NK cells, reflecting the notion that CALR can bind natural cytotoxicity triggering receptor 1 (NCR1, an NK cell-activating receptor [NKAR] best known as NKp46).[92] While an implication for NK cells in the clinical benefits experienced by patients with AML exposing abundant CALR at the blast surface has been reported,[93] the actual contribution of this latter mechanism to camouflage as elicited by defects in CALR exposure remains to be investigated. Finally, it should be noted that defective CALR exposure also promotes coercion by enabling the phosphatidylserine (PS)-driven clearance of dying cells by macrophages, an immunologically silent process commonly known as efferocytosis (see in the following text).[94–97]

Collectively, these observations highlight several mechanisms that camouflage cancer cells from the immune system by interfering with chemoattraction and APC-dependent phagocytosis.

Exclusion

At least in some instance, malignant cells evade immunosurveillance by generating a physical barrier that impedes immune effector cell recruitment to the TME. Such a camouflage mechanism mainly stems from TME remodeling as mediated by specific immune and stromal cells or from the reconfiguration of the extracellular matrix (ECM).

Three major cell populations of the TME that actively promote exclusion and consequently resistance to ICI-based immunotherapy[98] are cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), and tumor-associated neutrophils (TANs). Specifically, CAFs have been involved in the excluded phenotype and resistance to ICIs in patients with metastatic urothelial cancer and CRC, two settings in which CAF-derived transforming growth factor β 1 (TGFB1) promotes the confinement of $CD8^+$ CTLs inside CAF- and collagen-enriched peritumoral stromal regions.[99,100] Importantly, in syngeneic mouse models of these tumors, pharmacologically blocking TGFB1 resulted in unleashed CTL responses and improved sensitivity to ICI-based immunotherapy,[99,100] suggesting that TGFB1 and/or its receptors may constitute targets for the development of therapeutic strategies to limit exclusion-based camouflage. Similar findings, although without a clear implication for CAFs, have been obtained in patients with HGSOC bearing a specific mutational signature linked to foldback-inversion.[27] Along similar lines, patients with lung squamous-cell carcinomas exhibiting an excluded phenotype have been shown to experience inferior disease outcome as compared to patients with abundant tumor infiltration by $CD8^+$ CTLs.[101] In this latter setting, though, TAMs were the major contributors to exclusion, and blocking them with a small molecule specific for colony stimulating factor 1 receptor (CSF1R) restored the $CD8^+$ CTLs to tumor islets and ICI sensitivity, at least in a syngeneic mouse model of the disease.[101] However, in none of the aforementioned setting the mechanisms through which neoplastic cells educate CAFs or TAMs to establish exclusion have been clearly elucidated. Conversely, cancer cell-derived chitinase-3-like protein 1 (CHI3L1) has been shown to promote exclusion in triple negative breast cancer (TNBC), at least in part by favoring the recruitment of TANs to the TME and their ability to produce neutrophil extracellular traps (NETs),[102] i.e., extracellular protrusions containing chromatin and granule proteins that are generally involved in antimicrobial defense.[103] Similar findings have been obtained in preclinical models of melanoma and CRC, although in these settings TANs were reportedly recruited to the TME by cancer cell-derived CXCL8,[104] as well as in pancreatic ductal adenocarcinoma (PDAC) models, a setting in which immature and overall immunosuppressive neutrophil-like cells commonly known as polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) appeared to infiltrate neoplastic lesions via CXCL1 secretion by malignant cells and to establish exclusion upon the secretion of tumor necrosis factor (TNF).[105]

In melanoma, at least two mechanisms of exclusion have been documented. On the one hand, preclinical and clinical findings indicate that catenin beta 1 (CTNNB1) overexpression and consequent hyperactivation of WNT signaling promotes the establishment of an excluded phenotype in melanoma upon failed recruitment of $CD103^+$ conventional type I dendritic cells (cDC1s),[106] which are central orchestrators of anticancer

Box 1. Hypoxia and metabolic coercion

Vasculature defects causing at least some degree of hypoxia are common to most (if not all) solid tumors and have been consistently associated with immunosuppression.[276,439] Hypoxia promotes indeed the transcriptional activity of hypoxia inducible factor 1 subunit alpha (HIF1A) in malignant cells, which has multiple immunosuppressive consequences (detailed in the main text), including (1) a pronounced shift from oxidative mitochondrial metabolism to glycolysis coupled with abundant lactate secretion; (2) the secretion of vascular endothelial growth factor A (VEGFA); (3) the upregulation of ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD1, best known as CD39), ectonucleotidase 5′-nucleotidase ecto (5NTE, best known as CD73) and adenosinergic receptors[279,439]; as well as (4) the release of chemokines that either recruit immunosuppressive cells to the TME or sequester immune effector cells in hypoxic tumor regions while promoting their functional inhibition.[247,248] Of note, hypoxia has also direct inhibitory effects on tumor-infiltrating immune cells. For instance, hypoxic conditions have been associated with the upregulation of CD39 on intratumoral $CD8^+$ CTLs, resulting in accrued adenosinergic signaling and consequent immunosuppression.[440] Along similar lines, hypoxia reportedly promotes mitochondrial fragmentation in NK cells, hence compromising their effector functions, via a mechanism involving mechanistic target of rapamycin (MTOR) and dynamin 1 like (DNM1L).[441] Finally, tumor-targeting γδ T cells have been shown to be particularly sensitive to hypoxia, at least in preclinical models of glioblastoma (GBM).[442] Thus, hypoxia is a major factor underlying immune evasion in solid tumors, reflecting not only the activation of immunosuppressive mechanisms in malignant cells, but also the direct inhibition of intratumoral immune effectors.

immunity.[107,108] On the other hand, single-cell RNA sequencing studies suggested that melanoma cells can drive exclusion by a mechanism centered on cyclin-dependent kinase 4/6 (CDK4/6) signaling.[109] However, while in patients with melanoma a signature of CDK4/6 activation has been correlated with sensitivity to ICIs targeting programmed cell death 1 (PDCD1, best known as PD-1),[109] CDK4/6 inhibitors currently available for clinical use are only approved for advanced/metastatic hormone receptor (HR)-positive breast cancer,[110] implying that the value of these agents combined with ICIs remains to be established. Moreover, whether any exclusion-relevant link exists between WNT and CDK4/6 signaling has not been formally investigated.

Recent data indicate that phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta (PIK3CB), which is often hyperactivated in HR^+ breast cancer,[111] is also involved in the reclusion of $CD8^+$ CTLs to the periphery of mouse mammary carcinomas elicited by the loss of two phosphatase and tensin homolog (*Pten*) and transformation related protein 53 (*Trp53*), at least in part through a mechanism that involves suppressed STAT3 signaling.[112] Whether these observations are relevant for human HR^+ BC, however, remains to be clarified. Along similar lines, whether the ability of receptor-interacting protein kinase 2 (RIPK2) and proline isomerase (PIN1) to favor the establishment of a desmoplastic stroma coupled with limited ICI sensitivity in syngeneic models of PDAC[42,113] can be targeted for the development of novel therapeutic strategies against exclusion that can be translated to clinical testing is unclear.

Besides alterations in collagen abundance (as mediated by CAFs, mentioned previously), changes in its spatial arrangement also participate in exclusion. For instance, discoidin domain receptor 1 (DDR1) expression by TNBC cells has been shown to favor a parallel orientation of collagen fibers, *de facto* reducing the accessibility of the TME to immune effector cells.[114] Interestingly, in the same disease setting, T cell infiltration exhibits at least some degree of spatial heterogeneity, with subsets of quiescent stem-like cancer cells escaping immune recognition through the formation of immunosuppressive hypoxic niches enriched in CAFs that exhibit signatures of collagen-deposition pathways and an excluded phenotype.[115] That said, hypoxia is a major mechanism of coercion (Box 1) implying that the actual contribution of collagen deposition and physical CTL exclusion to these observations requires direct experimental verification.

Altogether, exclusion stands out as a major mechanism through which malignant cells camouflage from the host immune system. That said, whether exclusion can be targeted therapeutically in support of restored immunosurveillance and improved ICI sensitivity remains to be clinically demonstrated.

COERCION

Malignant cells that fail at camouflage (and hence are found and identified as transformed by the immune system) can evade anticancer immunity by suppressing the activity of immune effector cells including (but potentially not limited to) DCs, NK cells, T_H1-polarized $CD4^+$ T cells, and $CD8^+$ CTLs, as well as by promoting the activity of immunosuppressive cells such as $CD4^+CD25^+FOXP3^+$ regulatory T (T_{REG}) cells, specific TAM subsets, and MDSCs. Such a coercive activity can be the result of numerous alterations that involve shifts in the expression of immunomodulatory ligands on the cancer cell surface, defects in DAMP or pro-inflammatory cytokine signaling and/or the release of immunomodulatory metabolites in the TME (Figure 3).

Alterations in immunomodulatory ligands

Most neoplastic cells are characterized by an altered surface phenotype that encompasses reduced MHC levels in support of camouflage (mentioned previously) as well as changes in the expression of ligands for immune cell receptors with immunostimulatory or immunosuppressive effects.

PD-L1

CD274 (best known as PD-L1) is arguably the best characterized surface molecule that cancer cells harness in support of direct coercion, largely reflecting its ability to suppress the effector functions of $CD8^+$ CTLs,[116] NK cells,[117] and at least some myeloid cells[118] upon interaction with the co-inhibitory receptor PD-1, which is normally expressed in the context of immune activation. PD-L1 is also abundantly expressed by tumor-infiltrating myeloid cells, which also contribute to local immunosuppression.[119] As most normal cells, cancer cells upregulate PD-L1 in response to (mostly CTL-derived) IFNG, as part of a

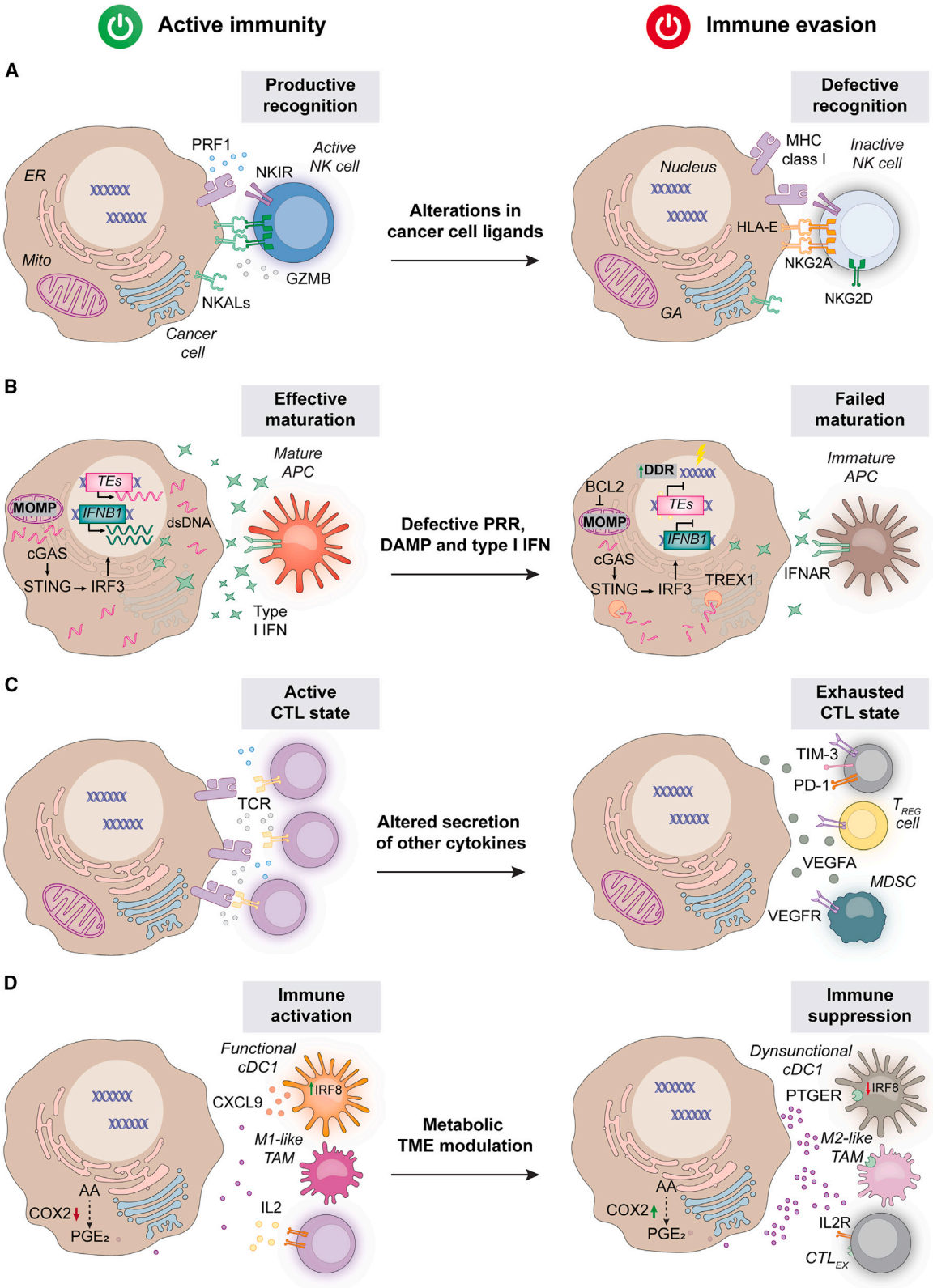

Figure 3. Coercion in cancer immune evasion

Developing neoplasms often acquire a number of alterations that actively inhibit tumor-targeting immune responses, either directly—by quenching the activity of immune effector cells, such as $CD8^+$ cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells—or indirectly—by promoting the regulatory functions of their

(legend continued on next page)

physiological mechanism that ensures the resolution of immune responses,[119] which is in line with the notion that most malignancies with an abundant $CD8^+$ CTL infiltrate are sensitive to ICIs targeting PD-1 or PD-L1.[120] Moreover, not only genetic variants structurally disrupting the 3′-untranslated region (UTR) of *CD274* are frequent in hematological malignancies, culminating with increased mRNA levels of *CD274* in support of immune evasion,[121] but *CD274* is often amplified across a variety of solid tumors, correlating with increase PD-L1 expression on the surface of malignant cells.[122]

PD-L1-mediated immunoevasion by breast CSCs has also been associated with increased transcription at the *CD274* locus upon removal of repressing marks from DNA and histone in the promoter region.[123] Importantly, such an epigenetic regulation of *CD274* expression can be targeted with Food and Drug Administration (FDA)-approved epigenetic modifiers such as azacitidine and decitabine, at least preclinically, resulting in increased PD-L1 expression and restored ICI sensitivity across cancer types.[124,125] Moreover, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a like 1 (SMARCAL1, a DNA damage response [DDR] factor) promotes PD-L1 expression by enhancing chromatin accessibility at the *CD274* locus with a mechanism involving Jun proto-oncogene, AP-1 transcription factor subunit (JUN).[126] Of note, PD-L1 expression levels can also be controlled at translation. Specifically, malignant cells can boost *CD274* translation by a mechanism involving eukaryotic translation initiation factor 4E (EIF4E) activation, as shown in MYC- and KRAS-driven liver cancer,[127] or impaired heme synthesis and consequent ISR signaling, as shown in lung cancer.[128]

At least in some tumor types, PD-L1 expression is also regulated by protein stabilization. For instance, the interleukin 6 (IL6)-dependent activation of Janus kinase 1 (JAK1) in liver cancer cells has been shown to result in PD-L1 phosphorylation and stabilization upon N-glycosylation as catalyzed by STT3 oligosaccharyltransferase complex catalytic subunit A (STT3A).[129] A similar mechanism has been shown to operate in breast cancer cells undergoing the epithelial-to-mesenchymal transition (EMT)—a dedifferentiation process associated with increased stemness and metastatic potential—upon increased WNT signaling.[130] Moreover, PD-L1 is stabilized in multiple tumor types by CKLF-like MARVEL transmembrane domain containing protein 6 (CMTM6), which directly binds PD-L1 at the plasma membrane and in recycling endosomes to prevent its lysosomal degradation.[131,132] Of note, at least in melanoma, PD-L1 has been shown to compete with CD58 (a ligand for the co-stimulatory receptor CD2) for CMTM6, with defects in CD58-CD2 axis promoting immune evasion.[132] PIN1 inhibition also appears to promote PD-L1 stabilization in PDAC, presumably through a mechanism that involves suppressed lysosomal degradation.[113]

Finally, PD-L1 appears to respond to a variety of stress conditions. For instance, reduced adenosine signaling via adenosine receptor A1 (ADORA1) reportedly promotes PD-L1 expression on melanoma cells via the stress-responsive transcription factor activating transcription factor 3 (ATF3).[133] Moreover, a switch to increased glucose consumption (as occurring in hypoxic tumor area) has been linked to PD-L1 upregulation in GBM cells, through a mechanism involving hexokinase 1 (HK2) and nuclear factor kappa B (NF-κB).[134]

In summary, while various ICIs targeting PD-L1 or PD-1 are currently available for clinical use, additional targets may exist to regulate this coercion mechanism via small molecules rather than monoclonal antibodies.

NK cell-interacting ligands

Neoplastic cells can evade elimination NK cells by downregulating a number of NK cell-activating ligands (NKALs) such as MHC class I polypeptide-related sequence A (MICA), MHC class I polypeptide-related sequence B (MICB), and UL16 binding proteins (ULBPs).[3] This is particularly relevant for cancer cells expressing reduced MHC class I levels to camouflage from $CD8^+$ CTLs, knowing that MHC class I is major NK cell-inhibitory ligand (NKIL).[3] Thus, MCC cells can avoid NK cell cytotoxicity through epigenetic silencing of *MICA* and *MICB* upon histone hhypoacetylation at their promoter region, a process that could be reverted upon pharmacological inhibition of histone deacetylases (HDACs).[135] Likewise, GBM cells have been shown to epigenetically silence MICA, MICB, and ULBPs in an EZH2-dependent manner,[136] while glioma cells appear to achieve a similar coercion via the histone demethylase lysine demethylase 1A (KDM1A, also known as LSD1).[137] In leukemic stem cells (LSCs) from patients with AML, the transcriptional repression of NKALs has been attributed to poly-ADP-ribose polymerase 1 (PARP1), a component of the DNA damage machinery that can be targeted by FDA approved inhibitors.[138] Finally, multiple cancer cells evade NK cell activation by promoting the proteolytic degradation or membrane shedding of NKALs upon overexpressing protein disulfide isomerase (PDI)[139,140] or various matrix metalloproteinases.[141,142]

Of note, malignant cells can coerce NK cells via the overexpression of various NKILs, notably canonical MHC class I

immunosuppressive counterparts, such as $CD4^+CD25^+FOXP3^+$ regulatory T (T_{REG}) cells. The alterations encompass (1) shifts in the expression of immunomodulatory ligands, as exemplified by changes in the expression pattern of NK cell-activating ligands (NKALs) or NK cell-inhibitory ligands (NKILs) (A); (2) defects in pattern recognition receptor (PRR), damage-associated molecular pattern (DAMP) or type I interferon (IFN) signaling, as exemplified by a variety of mechanisms that actively suppress viral mimicry (B); (3) alterations in the cancer cell secretome that affect cytokines other than type I IFN, as exemplified by the oversecretion of vascular endothelial growth factor A (VEGFA) (C); and (4) by a number of metabolic alterations that ultimately impact immune cell functions, such as the abundant secretion of prostaglandin E_2 (PGE_2; D). AA, arachidonic acid; APC, antigen-presenting cell; $CALR^{MUT}$, mutant CALR; CGAS, cyclic GMP-AMP synthase; cDC1, conventional type I dendritic cell; COX2 (official name: PTGS2) prostaglandin-endoperoxide synthase 2; CTLA4; cytotoxic T lymphocyte-associated protein 4; CXCL9, C-X-C motif chemokine ligand 9; CTL_{EX}, exhausted cytotoxic T lymphocyte; DDR, DNA damage response; dsDNA, double-stranded DNA; ER, endoplasmic reticulum; GA, Golgi apparatus; GZMB, granzyme B; IFNAR, interferon (alpha and beta) receptor; IFNB1, interferon beta 1; IL2, interleukin-2; IL2R, interleukin-2 receptor; IRF, interferon regulatory factor; MDSC, myeloid-derived suppressor cell; MOMP, mitochondrial outer membrane permeabilization; NKG2A (official name: KLRC1), killer cell lectin like receptor C1; NKG2D (official name: KLRK1), killer cell lectin like receptor K1; NKIR, NK cell-inhibitory receptor; PD-1 (official name: PDCD1), programmed cell death 1); PRF1, perforin 1; PTGER, prostaglandin E receptor; STING (official name: STING), stimulator of interferon response cGAMP interactor 1; TAM, tumor-associated macrophage; TCR, T cell receptor; TE, transposable element; TIM-3 (official name: HAVCR2), hepatitis A virus cellular receptor 2; TME, tumor microenvironment; TREX1, three prime repair exonuclease 1; VEGFR (official name: KDR), kinase insert domain receptor.

molecules as well as their non-canonical counterparts such as HLA-E,[3] as reported for a variety of solid and hematological malignancies.[143,144] Since this would come at the cost of potentially losing camouflage from CD8$^+$ T cells, it is tempting to speculate that cancer cells may benefit from reduced MHC class I levels (to camouflage from adaptive immunity) but not absent (to coerce innate immunity as mediated by NK cells). Alternatively, it is plausible that different tumors (or different areas of the same malignant lesion) may preferentially develop camouflage vs. coercion strategy depending on the type of immune pression they are facing. Despite these and other unknowns, it is worth noting that the interaction between HLA-E and its cognate NK cell-inhibitory receptor (NKIR), namely killer cell lectin like receptor C1 (KLRC1, best known as NKG2A) has been harnessed for the development of a monoclonal antibody (monalizumab)[145,146] that is now under clinical development (see in the following text). Conversely, the development of pharmacological strategies targeting killer cell immunoglobulin like receptor, two Ig domains and long cytoplasmic tail 1 (KIR2DL1), KIR2DL2, and KIR2DL3 including the monoclonal antibody IPH2101 has been discontinued after early phase clinical trials pointing to a paradoxical reduction in NK cell activity.[147] The reasons for this unexpected finding remain to be formally elucidated.

In summary, targeting the mechanisms through which cancer cells coerce NK cells stands out as a promising strategy to circumvent immune evasion, especially for malignancies that exhibit superior sensitivity to NK cell-mediated immunosurveillance (e.g., hematological tumors).

Other immunomodulatory ligands

Several other surface proteins are harnessed by malignant cells to coerce CD8$^+$ T cells, NK cells, and APCs. For instance, in PDAC models, overexpression of PVR cell adhesion molecule (PVR, also known as CD155) has been shown to promote and sustain immune escape upon inhibition of the T cell and NK cell co-inhibitory receptor T cell immunoreceptor with Ig and ITIM domains (TIGIT).[148] Moreover, a prolonged interaction between human type 2 innate lymphoid cells (ILC2s) and CD155$^+$ AML cells impairs the lytic activity of the former by downregulating CD226 (also known as DNAM-1) and granzyme B (GZMB), *de facto* facilitating immune evasion.[149] In AML, LSCs display the epitranscriptomic activation of different co-inhibitory ligands for T cells, including leukocyte immunoglobulin-like receptor B4 (LILRB4), a process that is mediated by the RNA N6-methyladenosine (m6A) demethylase FTO alpha-ketoglutarate dependent dioxygenase (FTO).[150]

In breast cancer cells, B7-H4 is stabilized via glycosylation, leading to immunosuppression and resistance to ICD inducers via a mechanism that also involves eIF2α dephosphorylation (aforementioned).[84] Hypoxic liver cancer cells overexpress galectin 9 (LGALS9), which suppresses T cell responses via the co-inhibitory receptor hepatitis A virus cellular receptor 2 (HAVCR2, best known as TIM-3),[151] through a mechanism involving the lysosomal degradation of the negative LGALS9 regulator nuclear transcription factor, X-box binding 1 (NFX1) by a carnosine synthase 2 (CARNS2) isoform.[152]

Importantly, CD8$^+$ CTLs and NK cells are not the sole targets for coercion by cancer cells via immunomodulatory surface ligands. Indeed, malignant cells actively evade phagocytosis by APCs including DCs by upregulating the expression of CD47 on the plasma membrane, which directly counteracts the pro-phagocytic activity of surface-exposed CALR.[153] More specifically, CD47 suppresses phagocytosis (and hence limits the initiation of antitumor immunity) by interacting with signal regulatory protein alpha (SIRPA) on APCs and masking the pro-phagocytic ligand SLAM family member 7 (SLAMF7) on cancer cells.[154,155] CD47 is upregulated in GBM cells via a fatty acid-dependent mechanism that involves the acetylation of RELA proto-oncogene, NF-kB subunit (RELA) and correlates with poor patient prognosis.[156] Likewise, elevated CD47 levels have been linked with dismal disease outcome in three independent cohorts of adult patients with AML.[157] Of note, CD47 appears to be particularly elevated in LSCs,[157,158] potentially constituting an actionable target for this highly tumorigenic leukemia cell subpopulation. Moreover, CD47 can be upregulated in response to ICD induction. For instance, in syngeneic osteosarcoma models, treatment with ICD-inducing chemotherapy has been associated with upregulation of solute carrier family 7 member 8 (SLC7A8, best known as LAT2) coupled with enhanced uptake of leucine and glutamine, culminating with mechanistic target of rapamycin complex 1 (mTORC1) signaling and *Cd47* transactivation.[159] Of note, CD24 also appears to provide robust anti-phagocytic signals to myeloid cells upon interacting with sialic acid binding Ig like lectin 10 (SIGLEC10).[160] At least in part, the ability of CD24 and perhaps other surface proteins expressed by cancer cells to limit phagocytosis may explain why several clinical studies testing CD47-targeting agents in patients with cancer have failed to document consistent efficacy so far.[161]

Collectively, these observations exemplify the existence of multiple immunomodulatory ligands other than PD-L1 that cancer cells harness to coerce the immune system, some of which are being actively pursued for the development of novel therapeutic interventions (see in the follwoing text).

Defective PRR, DAMP, and type I IFN signaling

In many malignant cells, the molecular mechanisms that underlie the emission of immunostimulatory DAMPs and cytokines, be them related to ICD or not, are dysfunctional or actively counterbalanced, resulting in the establishment of microenvironmental conditions that are not permissive for anticancer immunity.

Defective CGAS-STING1 signaling

Cyclic GMP-AMP synthase (CGAS) is a sensor of cytosolic double-stranded DNA (dsDNA) that elicits pro-inflammatory transcriptional programs executed by interferon regulatory factor 3 (IRF3), IRF7, and NF-κB upon activation of stimulator of interferon response cGAMP interactor 1 (STING1, best known as STING) and consequent TANK binding kinase 1 (TBK1) signaling.[162] Defects in CGAS-STING signaling considerably impair the ability of stressed and dying cancer cells to attract and activate immune effector cells downstream of IRF3-, IRF7-, and NF-κB-dependent cytokines, notably interferon beta 1 (IFNB1).[163]

A number of common oncogenic events have been associated with compromised CGAS-STING signaling in malignant cells, largely corroborating the importance of immunoevasion for overt tumor progression. For instance, loss of kelch like ECH associated protein 1 (KEAP1) promotes lung cancer resistance to immunotherapy by stabilizing EMSY transcriptional repressor, BRCA2 interacting (EMSY), hence suppressing CGAS-STING

signaling by a mechanism that can be reverted upon administration of pharmacological STING agonists.[164] Moreover, in mammary tumors, mutant tumor protein p53 (TP53, best known as p53) has been shown to physically interfere with the interaction between STING and TBK1, *de facto* promoting immunoevasion via defective IRF3 signaling.[165]

Several epigenetic mechanisms through which malignant cells suppress CGAS-STING signaling have also been documented. For instance, loss of serine/threonine kinase 11 (STK11, best known as LKB1) enhances immunoevasion and resistance to ICIs in KRAS-driven lung cancer by promoting the hyperactivation of DNMT1 and EZH2, resulting in epigenetic *STING1* silencing.[166] Along similar lines, hypermethylation of the *STING1* promoter and enhancers has been shown to promote immune evasion in dormant lung cancer cells.[167] Moreover, in melanoma and head and neck squamous cell carcinoma (HNSCC), CGAS expression is epigenetically regulated by histone methylases, including protein arginine methyltransferase 5 (PRMT5) and SUV39H1 histone lysine methyltransferase (SUV39H1), or components of supramolecular histone ubiquitin transferases complexes, such as BMI1 proto-oncogene, polycomb ring finger (BMI1), a core constituent of the polycomb repressive complex 1 (PRC1).[168–170] Lung cancer cells appear to silence *IRF3* and *IRF7* by promoter hypermethylation, resulting in decreased type I IFN signaling and reduced sensitivity to ICIs, an immunoevasive mechanism that can be at least in part reverted with hypomethylating agents.[125] Along similar lines, both lung and breast malignancies have been shown to exhibit defects in the type I IFN signal transducers STAT1 and STAT2,[171,172] which—at least in the latter cancer type—are epigenetically established by EZH2 and hence can be effectively targeted with pharmacological EZH2 inhibitors.[172] Finally, melanoma-initiating cells appear to promote the inhibitory dephosphorylation of STAT1 through a mechanism mediated by the epitranscriptomic stabilization of T cell protein tyrosine phosphatase (TCPTP).[40]

Post-translational CGAS and STING modifications have also been shown to endow malignant cells with immunoevasive properties. For instance, melanoma cells reportedly coerce immune effector cells upon losing expression of the oncosuppressor death-associated protein kinase 3 (DAPK3), which—among other functions—stabilizes STING via polyubiquitination.[173] Along similar lines, the non-enzymatic, inactivating acetylation of CGAS as promoted by aspirin,[174] as well as the degradation of the CGAS-derived STING activator 2′3′-cyclic GMP-AMP (cGAMP) as mediated by sphingomyelin phosphodiesterase acid like 3A (SMPDL3A),[175] or ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1),[176–178] have all been linked to reduced CGAS signaling, although only the latter has been formally associated with suppressed anticancer immunity.

These observations indicate that the direct repression of CGAS and STING signaling endow malignant cells with immunoevasive properties. Importantly, the same signaling pathway can also be disrupted by numerous indirect mechanisms, as described here in the following text.

Impaired viral mimicry

CGAS signaling is elicited by the ectopic accumulation of dsDNA in the cytosol, a process that is considerably more effective when dsDNA is naked (i.e., does not contain histones),[179–181] and hence originates from mitochondria as a consequence of apoptotic mitochondrial outer membrane permeabilization (MOMP) (or viral infection).[182–185] Cancer cells often evolve strategies to avoid or compensate for the cytosolic accumulation of endogenous dsDNA, including (but not limited to) an increased propensity to repair nuclear DNA damage in the absence of potentially interferogenic side products, to repress endogenous retroviruses (ERVs) and other transposable elements (TEs), to preserve mitochondrial integrity and to actively degrade cytosolic nucleic acids.

Several components of the DDR, apparatus have been shown to prevent CGAG-STING signaling.[186] These include various proteins that have already been established or are being actively investigated as targets for (novel) anticancer (immuno)therapy, such as PARP1 (for which several inhibitors have already been approved for use in humans), as well as ATR serine/threonine kinase (ATR), and ATM serine/threonine kinase (ATM).[186] An abundant preclinical literature indicates indeed that inhibiting PARP1, ATM, and ATR results in the accumulation of interferogenic nucleic acids in the cytosol of malignant cells, culminating with the STING-dependent restoration of ICI sensitivity across a number of cancer types.[187–190] While similar observations have recently been extended to SMARCAL1 and DExD/H-box helicase 9 (DHX9),[126,191] pharmacological strategies to target these two DDR components to avert immune evasion downstream suppressed CGAS activation by cytosolic dsDNA have not entered clinical development yet. Moreover, at least in some settings including skin cancer, some epigenetic modifiers like KDM4A have been shown to limit the accumulation of potentially interferogenic nucleic acids in the cytosol of malignant cells by strengthening the DDR,[192] but the precise molecular mechanisms remain to be elucidated.

Malignant cells, especially CSCs, silence the expression of ERVs and other TEs that may not only drive robust type I IFN responses via CGAS or cytosolic RNA sensors like RNA sensor RIG-I (RIGI) or interferon induced with helicase C domain 1 (IFIH1) but may also generate neoantigens.[193,194] In multiple solid and hematological malignancies, both DNA and histone methyltransferases contribute to TE silencing, including DNMT1, SETDB1, and HDACs, which deposit repressive DNA methylation, histone methylation, and histone acetylation marks within TE regions, *de facto* limiting type I IFN responses.[195–199] A similar ERV-repressing role has been ascribed to KDM1A and PHD finger protein 8 (PHF8, also known as KDM7B).[200,201] That said, the histone methyltransferase nuclear receptor binding SET domain protein 1 (NSD1) appears to transactivate, rather than repress, ERVs in skin cancer,[202] indicating that—at least in some settings—coercion as promoted by TE repression is driven by an unbalanced activity of epigenetic modifiers. Along similar lines, GBM CSCs appear to repress interferogenic TEs by a unique mechanism involving increased histone H4 lysine crotonylation arising from reprogrammed lysine catabolism, which also results in changes on histone acetylation and methylation marks on TEs.[203] Moreover, both p53 and CDK4/6 have been involved in the transcriptional regulation of ERVs and consequent type I IFN responses,[204,205] hence representing promising targets for the development of pharmacological strategies to avert coercion, especially since no less than three distinct CDK4/6 inhibitors are currently approved for use in patients with advanced or metastatic HR^+ breast cancer.[110]

A major mechanism through which neoplastic cells avert the cytosolic accumulation of potentially interferogenic dsDNA is by ensuring a tight mitochondrial checkpoint. This is achieved not only upon the overexpression of endogenous inhibitors of the BCL2 apoptosis regulator (BCL2) family, which is common across a variety of tumors,[206] but also upon the proficient degradation of permeabilized mitochondria via a specialized variant of autophagy called mitophagy.[207] In line with this notion, both pharmacological and genetic strategies targeting the BCL2 system have been associated with increased CGAS-STING signaling in malignant cells, especially (but not exclusively) in the context of caspase inhibition (see in the following text).[183,184,208,209] Intriguingly, at least in some settings, MOMP does not only promote CGAS activation via cytosolic DNA but also initiates a ubiquitin-dependent pro-inflammatory pathway that involves inhibitor of nuclear factor kappa B kinase regulatory subunit gamma (IKBKG, best known as NEMO) and culminates with NF-κB signaling.[210] Further corroborating the importance of the mitochondrial checkpoint for malignant cells to coerce their immune counterparts, both pharmacological and genetic inhibition of autophagy at large or mitophagy have been associated with accrued CGAS-STING signaling and superior disease control in preclinical models of breast cancer,[183] lung cancer,[211] and CRC.[212] Moreover, intact serine metabolism appears to be critical for the preservation of the mitochondrial immune checkpoint (see in the following text).[182] Interestingly, in macrophages the mitophagic degradation of permeabilized mitochondria has been involved in a negative feedback loop to extinguish NF-κB responses.[213] Whether this mechanism is operational in cancer cells, however, remains to be formally investigated.

Finally, neoplastic cells express some cytosolic nucleases that efficiently degrade potentially interferogenic nucleic acids. For instance, three prime repair exonuclease 1 (TREX1) has been shown to degrade cytosolic mtDNA,[214] as well as cytosolic dsDNA originating from ruptured micronuclei (which are common in tumors with elevated chromosomal instability [CIN]).[215] In line with this notion, TREX1 overexpression has been associated with suppressed CGAS-STING signaling and resistance to treatment in syngeneic preclinical models of breast cancer exposed to focal radiotherapy,[216] and lung cancer exposed to ICIs.[217] Ribonuclease H2 also limits the cytosolic accumulation of potentially interferogenic nucleic acids, especially so-called "R-loops" (three-stranded nucleic acids composed of a DNA:RNA hybrid and the associated non-template single-stranded DNA).[218] While it is likely that—at least in some settings—ribonuclease H2 may operate similar to TREX1 in promoting coercion and resistance to immunotherapy, this possibility remains to be explored. Intriguingly, it has recently been shown that MRE11 homolog, double-strand break repair nuclease (MRE11), a DNA double-strand break sensor, promotes CGAS activation by dsDNA upon favoring its dissociation from nucleosomes.[219] In this context, malignant cells appear to take advantage from reduced MRE11 levels, resulting in increased genome instability and immune suppression.[219] Supporting the clinical relevance of this coercion mechanism, reduced levels of the MRE11 signal transducer Z-DNA binding protein 1 (ZBP1) appear to correlate with poor disease outcome in a cohort of patients with TNBC.[219]

In summary, malignant cells not only can directly subvert CGAS-STING signaling but also can adopt a variety of strategies to minimize the availability of interferogenic nucleic acids, *de facto* limiting viral mimicry.

Defective DAMP signaling

The non-histone chromatin-binding protein high-mobility group box 1 (HMGB1) is one of the major ICD-associated DAMPs, and its microenvironmental accumulation mediates immunostimulatory effects upon binding to Toll-like receptor 4 (TLR4) and advanced glycosylation end-product specific receptor (AGER) on the surface of APCs or their precursors.[220,221] Experimental evidence indicates that neoplastic cells lose the expression of HMGB1 and other DAMPs during tumor progression, at least in the breast cancer setting.[64] Moreover, cancer cells engineered to lack HMGB1 fail to elicit anticancer immune responses upon exposure to ICD inducers in immunocompetent syngeneic host, largely via a coercion mechanism that could be reverted by intratumoral injection of a synthetic TLR4 agonist.[220,222] Along similar lines, human bladder cancer cells undergoing ICD upon exposure gemcitabine fail to release HMGB1 in the supernatant, hence failing to endow DCs with $CD8^+$ T cell cross-priming functions, at least in part owing to the release of the bioactive lipid prostaglandin E_2 (PGE_2) (see in the following text).[223] Intriguingly, it appears that the ISR-relevant kinase eukaryotic translation initiation factor 2 alpha kinase 3 (EIF2AK3, best known as PERK) restricts anticancer immunity in melanoma cells at least in part by inhibiting the release of HGMB1 and other DAMPs as a consequence of blocked paraptosis (which appears to be immunogenic).[224] Thus, PERK inhibitors may constitute promising tool to promote immunogenic paraptosis, at least in melanoma.

Coercion via defective DAMP signaling can also emerge from the secretion of immunosuppressive DAMPs. For instance, mouse melanoma and fibrosarcoma cells have been shown to avert anticancer immunity downstream of ICD by secreting gelsolin (GSN), which inhibits the binding of F-actin exposed on dying malignant cells to C-type lectin domain containing 9A (CLEC9A) on cDC1s, thereby preventing $CD8^+$ T cell cross-priming.[225] Similarly, fibrinogen-like protein 1 (FGL1) released by CRC cells reportedly binds the co-inhibitory receptor lymphocyte activating 3 (LAG3) on the $CD8^+$ CTL surface, hence suppressing their activation.[226] Importantly, the ICD-associated release of ATP provides chemotactic cues (mentioned previously) as well as immunostimulatory signals to APCs and their precursors, implying that defects in this pathway also constitute a source of coercion (see in the following text).

These observations exemplify the ability of malignant cells to coerce immune effector cells by altering DAMP signaling.

Apoptotic signaling

Neoplastic cells often succumb to unrecoverable perturbations of homeostasis via apoptosis, a caspase-regulated form of cell death with major physiological functions.[227] In line with the critical role of apoptosis in embryonic development and the maintenance of adult tissue architecture, though, caspase activation has multipronged immunosuppressive effects, even when apoptotic cell death ensues MOMP and hence is potentially associated with the abundant cytosolic accumulation of interferogenic mtDNA. Indeed, post-mitochondrial caspases including caspase 3 (CASP3) and its major activator CASP9

have been shown to suppress MOMP-driven type I IFN secretion in a variety of experimental models, including preclinical models of breast and CRC.[208,209,228–230]

Such a coercion mechanism has been attributed to the ability of CASP3 to (1) catalyze the proteolytic inactivation of CGAS, IRF3 and mitochondrial antiviral signaling protein (MAVS), a signal transducer involved in RIGI-dependent RNA sensing[231] and (2) accelerate the terminal inactivation of otherwise still metabolically active (and hence type I IFN-secreting) dying cancer cells.[232] Moreover, CASP3 promotes the apoptosis-associated exposure of PS on the surface of dying cells coupled with the secretion of the macrophage chemoattractant lysophosphatidylcholine (LPC), hence facilitating the rapid efferocytic removal of dying cells and their corpses by macrophages.[94–97] The immunologically silent nature of efferocytosis is further enforced by CASP3 activation in dying cancer cells as a consequence of PGE_2 secretion (see in the following text).[233]

Thus, developing tumors harness apoptotic cell death to prevent the initiation of anticancer immunity by dying malignant cells. Along with the ever more accepted notion that post-mitochondrial caspases are dispensable for cell death after widespread MOMP—but only control its kinetic and immunological manifestations[234]—these observations point to caspases as to potential target to promote therapeutically relevant anticancer immunity.

Chronic type I interferon signaling

At least some neoplastic cells can coerce type I interferon signaling in support of local immunosuppression and accelerated disease progression, most likely reflecting the fundamental difference between acute and resolving inflammatory processes (which generally promote immunosurveillance) versus chronic and indolent inflammation (which generally supports immunoevasion).[235] For instance, malignant cells with elevated CIN levels have been shown to evade immunosurveillance despite high levels of cytosolic DNA by rewiring the CGAS-STING pathway from abundant type I IFN production to low-grade inflammation, resulting in the EMT and accrued metastatic dissemination.[236–239] Along similar lines, chronic and indolent type I IFN signaling has been shown to promote stemness, disease progression, and immune evasion in preclinical models of CRC, TNBC, and melanoma.[240,241] Consistent with this notion, genetic signatures of type I IFN signaling have been associated to cancer stemness, immunosuppression, and poor patient outcomes across multiple cohorts of patients with cancer.[228,242]

Thus, while robust and acute type I IFN signaling is fundamental for tumor-targeting immune responses (see previously), malignant cells normally benefit from weak and chronic type I IFN signaling, at least in part reflecting the establishment of a low-grade inflammatory milieu associated with immunosuppression.

Altered secretion of other cytokines

Multiple tumors evade anticancer immunity by alterations in their secretome that involve an accrued production of anti-inflammatory cytokines and/or a defective release of pro-inflammatory factors other than type I IFN.

Secretion of anti-inflammatory cytokines

Multiple cancer types can secrete cytokines that favor the establishment of local and/or systemic immunosuppression. For instance, prostate cancer cells have been shown to secrete CCL2 downstream of PRC1-dependent epigenetic alterations, culminating with the recruitment of immunosuppressive M2-like TAMs and T_{REG} cells, which facilitate tumor dissemination.[243] Similarly, in mammary tumors, the loss of the tumor suppressor G protein subunit alpha 13 (GNA13) promotes CCL2 expression and secretion, attracting M2-like TAMs.[244] Moreover, PDAC cells have been shown to secrete abundant levels of CCL5 upon STAT1 activation in response to microenvironmental adenosine (see in the following text), resulting in the establishment of local immunosuppression upon T_{REG} cell recruitment.[245] A similar CCL5-dependent mechanism has been documented to promote M2-like TAM recruitment in CRCs producing kynurenine (see in the following text).[246] Finally, ovarian cancer cells have been shown to recruit T_{REG} cells via CCL28, a mechanism that is elicited by hypoxia (Box 1).[247] Likewise, hypoxic GBM niches appear to secrete increased levels of CCL8, resulting in the sequestration of TAMs and tumor-infiltrating $CD8^+$ CTLs and their reprogramming toward an immunosuppressive state.[248]

Besides being a major player in exclusion-based camouflage (mentioned previously), TGFB1 also mediates potent immunosuppressive effects, *de facto* promoting coercion, across a variety of tumor types. For instance, MFSD2 lysolipid transporter A, lysophospholipid (MFSD2A) overexpression in gastric cancer cells has been shown to promote anticancer immune responses downstream of reduced PGE_2-driven TFGB1 secretion, hence increasing tumor sensitivity to ICIs.[249] Moreover, TFGB1 signaling in $CD4^+$ (but not $CD8^+$) T cells potently suppresses therapeutically relevant immune responses in preclinical models of breast carcinoma, at least in part reflecting an IL4-dependent (but not IFNG-dependent) tissue remodeling mechanism that culminates with cancer cell death.[250] Along similar lines, both TGFB1 and its relative inhibin subunit beta A (INHBA) have been implicated in the ability of irradiated breast cancer cells to coerce the TME in favor of suppressed anticancer immunity.[251,252] Accordingly, combining focal radiotherapy with a monoclonal antibody targeting multiple members of the TGFB1 family was well tolerated and demonstrated some clinical activity in a cohort of patients with metastatic breast cancer,[253] and strategies to inhibit this pathway are currently being investigated in clinical trials (see in the following text).

CXCL8 and IL33 are also harnessed by some cancer cells to promote local immunosuppression. For instance, tumor-derived CXCL8 has been implicated in the recruitment of both monocytic (M-) and PMN-MDSCs to the TME, resulting in suppressed T cell responses.[254] At least in some settings including preclinical models of cervical carcinoma, such an effect is mediated by serpin family B member 3 (SERPINB3),[255] which is frequently mutated in patients with melanoma responding to cytotoxic T lymphocyte-associated protein 4 (CTLA4) blockers.[256] The immunosuppressive role of IL33 has been documented in syngeneic models of lung cancer, breast cancer and melanoma exposed to an IL33 blocker.[257,258] That said, the transgene enforced overexpression of IL33 has also been associated with improved anticancer immunity in models of breast cancer and melanoma.[259] In line with this notion, IL33 expression as driven in mouse CRC and melanoma cells by the deletion of fragile X mental retardation protein (*Fmrp*), encoding an RNA binding protein, has been associated with restored tumor infiltration by $CD8^+$ CTLs and recovered ICI sensitivity (also involving a

Box 2. T cell exhaustion

In a number of pathophysiological settings, including (but not limited to) chronic viral infection and cancer, the sustained antigenic stimulation of $CD8^+$ cytotoxic T lymphocytes (CTLs), as occurring in the absence of target cell eradication, can promote terminal CTL dysfunction.[443] In cancer, such a dysfunctional state, which is commonly referred to as ''exhaustion'', is associated with the progressive loss of CTL cytotoxic and secretory functions, *de facto* enabling immune evasion, accelerated disease progression and resistance to a variety of therapeutic agents that operate (at least in part) by (re)instating immunosurveillance, including (but not limited to) immune checkpoint inhibitors (ICIs).[444] While *sensu stricto* exhaustion does not emerge from cancer cells but rather reflects chronic TCR signaling, developing neoplasms harness multiple phenotypic T cell changes associated with this process, notably the overexpression of co-inhibitory receptors including programmed cell death 1 (PDCD1, best known as PD-1), hepatitis A virus cellular receptor 2 (HAVCR2, best known as TIM-3) and T cell immunoreceptor with Ig and ITIM domains (TIGIT), to maximize immunosuppression in the tumor microenvironment upon the overexpression of their cognate ligands (see main text).[390,445,446] While exhaustion is largely dictated by epigenetic modifications encompassing the downregulation of transcription factor 7 (TCF7), a master regulator of T cell effector functions whose expression generally identifies CTL subsets that are sensitive to ICIs,[447] accumulating evidence suggests that terminal T cell exhaustion can be prevented, but most often not reverted.[443] This suggests that (immuno)therapeutic agents targeting exhaustion may need to be administered as early as possible during disease progression to effectively restore immunosurveillance. In line with this notion, neoadjuvant immunotherapy with ICIs has demonstrated superior efficacy in a number of oncological indications.[1]

CCL7-dependent camouflage mechanism).[260] Together, these observations potentially indicate that indolent IL33 signaling may be detrimental, while robust IL33 signaling beneficial, for anticancer immune responses, as in the case of type I IFN (mentioned previously).

Importantly, while vascular endothelial growth factor (VEGFA), which is the target of the FDA-approved monoclonal antibody bevacizumab,[261] has long been considered a purely angiogenic cytokine, it is now clear that VEGFA also mediates considerable immunosuppressive functions. For instance, VEGFA reportedly promotes the expansion of T_{REG} cells in syngeneic models of CRC and patients with metastatic CRC, as demonstrated by the T_{REG} cell-depleting effects of blocking VEGFA in either setting.[262,263] Similar findings have been documented in patients with glioblastoma receiving radiotherapy, temozolomide and bevacizumab.[264] Moreover, VEGFA (which is actively secreted by malignant cells especially in hypoxic tumor areas, see below) appears to promote T cell exhaustion (Box 2) by favoring the expression of co-inhibitory receptors including PD-1, TIM-3, and CTLA4 on their surface, at least in preclinical CRC models.[265] In line with this finding, combined VEGFA, PD-1, and angiopoietin 2 (ANGPT2) inhibition has been associated with a therapeutically relevant reprogramming of the TME involving increased $CD8^+$ CTL infiltration and reduced intratumoral MDSC levels in preclinical GBM models.[266] The therapeutic value of concomitantly blocking VEGFA and PD-1 signaling has already been confirmed in multiple phase III clinical trials enrolling patients with renal cell carcinoma (RCC).[267,268]

Defective release of pro-inflammatory cytokines other than type I IFN

Besides defects in the release of chemoattractants in support of camouflage and type I IFN-related cytokines in support of coercion (mentioned previously), some malignant cells often secrete limited amounts of other pro-inflammatory cytokines to promote local immunosuppression. For instance, breast, colorectal, and lung cancer cells release limited levels of interleukin 1B (IL1B), which inhibits the activation of tumor-infiltrating ILC3s in support of immune evasion.[79] Along similar lines, it is plausible that the detrimental effects of reduced ZBP1 levels in patients with TNBC[219] (mentioned previously) may impinge on limited inflammasome activation and IL1B secretion, knowing that ZBP1 promotes an inflammatory cell death modality commonly known as necroptosis.[269,270] That said, IL1B (and TNF) secretion by tumor-infiltrating immune cells has also been shown to elicit immunosuppressive CXCL8 secretion in a broad panel of human cancer cell lines,[271] pointing to at least some degree of context dependency in the immunomodulatory effects of IL1B.

Similar results have been documented for IL10. Indeed, while the presence of IL10-secreting macrophages as elicited by GABA-producing B cells has been associated with impaired anticancer immunity in preclinical models of CRC,[272] the administration of a half-life-extended IL10-Fc fusion protein considerably boosts the antitumor functions of $CD8^+$ CTLs via metabolic reprogramming, offering a potential combinatorial partner for ICI- and ACT-based immunotherapy.[273] In line with this notion, recombinant IL10 has been shown to improve $CD8^+$ CTL secretory and cytotoxic functions.[274] Similar observations have been obtained in a cohort of patients with advanced solid tumors receiving PEGylated IL-10 (pegilodecakin).[275] Specifically, pegilodecakin improved tumor infiltration by $CD8^+$ CTLs and their IFNG and GZMB expression levels while causing the expansion of previously undetectable circulating $CD8^+$ CTL clones up to 1%–10% of the total peripheral T cell repertoire.[275] These observations are reminiscent of the type I IFN and IL33 scenarios, pointing to a divergent immunomodulatory activity for indolent vs. robust signaling, at least in the TME.

In summary, malignant cells often acquire secretory alterations that endow them with the ability to coerce immune cells and establish robust immunosuppression in favor of disease progression.

Metabolic modulation of the TME

All cancer cells exhibit a considerable metabolic rewiring as compared to their normal counterparts.[276] While for long such metabolic alterations were interpreted as a pure consequence of the accrued trophic needs of malignant cells, it is now clear that several metabolic pathways that are altered in cancer actively promote immunosuppression.[277]

ATP and adenosine

Besides being a powerful chemoattractant (mentioned previously), extracellular ATP mediates immunostimulatory functions upon binding to purinergic receptor P2X 7 (P2RX7) on APCs or their precursors, which results in IL1B secretion upon inflammasome activation.[278] Thus, most of the immunological defects caused by defective ATP release by cancer cells (mentioned previously) may involve coercion (rather than camouflage only). That said, extracellular ATP hydrolysis and consequent adenosine accumulation mediates immunosuppressive effects that are mostly based on coercion. In line with this notion, most human tumors expressed increased levels of CD39 and CD73, resulting in prominent adenosinergic signaling on tumor-infiltrating immune cells.[279] This is particularly true for hypoxic tumor regions (Box 1), at least in part reflecting the ability of hypoxia inducible factor 1 subunit alpha (HIF1A) to transactivate *ENTPD1* and *NT5E*.[279] By binding to adenosine A2a receptor (ADORA2A) on the T cell surface, adenosine potently limits TCR signaling and IFNG production.[280]

Adenosine signaling has been consistently linked with disease progression and resistance to (immuno)therapy in a variety of preclinical tumor models. For instance, radiotherapy has been shown to drive the upregulation of CD73 on the surface of mouse breast cancer cells, an effect that could be circumvented in support of restored cDC1 tumor infiltration and recovered anticancer immunity with a CD73-targeting monoclonal antibody.[281] A similar immunosuppressive upregulation of CD73 (and PD-L1) has been documented in GBM CSCs exposed to repeated immunological pressure, resulting in the acquisition of a myeloid-like transcriptional profile dominated by IRF8 upregulation.[282] ADORA2A also appears to be upregulated on CAR T cells responding to mouse PDACs *in vivo*, resulting in limited efficacy owing to microenvironmental adenosine levels, a compensatory mechanism that can be circumvent by both genetic and pharmacological strategies targeting ADORA2A or CD73, also as a result of decreased CCL5-driven T_{REG} cell recruitment (mentioned previously).[245] Interestingly, the dual inhibition of CD73 and ADORA2A has proven more effective than either approach in promoting anticancer immunity in syngeneic mouse models of mammary cancer and melanoma.[283] This suggest that the global immunosuppressive effects of CD73 and ADORA2A do not only emerge from suppressed adenosinergic signaling via the latter, potentially involving (1) decreased ATP availability or (2) adenosinergic signaling via adenosine A2b receptor (ADORA2B).[59]

In summary, both extracellular ATP degradation and consequent adenosinergic signaling mediate robust coercive effects on the TME in various oncological settings. That said, various clinical studies have been performed to investigate the therapeutic potential of agents that limit adenosinergic signaling in patients with cancer, so far with limited success.[284]

Kynurenine

Tryptophan degradation is a prominent mechanism of immunosuppression within the TME, as primarily driven by the indoleamine 2,3-dioxygenase 1 (IDO1)- or tryptophan 2,3-dioxygenase (TDO2)-catalyzed conversion of tryptophan into kynurenine, a potently immunosuppressive metabolite.[285] While IDO1 is mostly expressed by myeloid cells of the TME,[285] some neoplastic cells can also produce kynurenine in support of local immunosuppression. For instance, CRC cells can secrete kynurenine through a mechanism that involves the upregulation of ubiquitin specific peptidase 14 (USP14), resulting in deubiquitination-dependent IDO1 stabilization.[286] In this setting, genetic or pharmacological inhibition of USP14 restored CTL activation and tumor sensitivity to ICIs targeting PD-1.[286] Immunoevasive CRCs have also been shown to exhibit TDO2 upregulation as driven by transcription factor 4 (TCF4) and WNT signaling, resulting in elevated kynurenine production and consequent recruitment of M2-like TAMs via an aryl hydrocarbon receptor (AHR)-dependent mechanism promoting CCL5 secretion.[246] Similarly, the secretion of kynurenine by glioma cells has been shown to inhibit the proliferation and functionality of $CD4^+$ and $CD8^+$ T cells via paracrine AHR signaling.[287]

Intriguingly, in preclinical melanoma models, IFNG release by tumor-infiltrating $CD8^+$ CTLs appears to upregulate the neutral amino acid transporter solute carrier family 1 member 5 (SLC1A5) on the surface of tumor repopulating cells (TRCs), resulting in increased tryptophan uptake and consequent kynurenine production.[288] In this context, TRCs overexpress both IDO1 and AHR, which endow them with capacity to evade cell death as initiated by IFNG and instead undergo dormancy (see in the following text).[288] Despite considerable expectations as set by the encouraging results of multiple phase II clinical trials, however, combining the IDO1 inhibitor epacadostat with the PD-1 blocker pembrolizumab failed to provide a clinical advantage as compared to pembrolizumab alone to patients with advanced melanoma enrolled in a large, randomized phase III clinical study.[289] While the precise reasons underlying these negative results remain to be understood, the enthusiasm around the use of IDO1 inhibitors as combinatorial partners for ICI-based immunotherapy in patients with cancer has considerably reduced as a consequence thereof.[290,291]

Of note, other IDO1-derived metabolites have been attributed potent immunomodulatory functions, including quinolinate, which accumulates in GBM to promoting TAM polarization toward an M1-like phenotype through glutamate ionotropic receptor NMDA type subunit 2B (GRIN2B), forkhead box O1 (FOXO1), and peroxisome proliferator activated receptor gamma (PPARG) signaling,[292] as well 3-hydroxy-L-kynurenamine (3-HKA), which, at least in non-oncological settings, inhibits the STAT1 and NF-κB signaling in DCs, thereby limiting their release of pro-inflammatory cytokines.[293] Whether these metabolites or the signaling pathways they elicit can be harnessed therapeutically to circumvent metabolic immune coercion remains to be determined.

Despite this unexplored possibility, tryptophan catabolism remains a core mechanism through which malignant lesions establish local immunosuppression. That said, additional work is required to understand the actual therapeutic potential of this pathway.

Glucose and glutamine

Anticancer immune responses are highly influenced by the metabolic competition for nutritional substrates, notably glucose and glutamine, in the TME.[277] For example, glucose consumption by ovarian cancer cells has been shown to limit its availability to $CD8^+$ CTLs, resulting in impaired glycolytic flux and effector functions.[294] A similar coercion mechanism has been observed in a syngeneic models of sarcoma, a setting in which ICI administration restored glucose availability in the TME, resulting in

increased glycolytic flux in T cells and therapeutically relevant IFNG secretion,[295] and lymphoma, in a scenario in which acetate supplementation was sufficient to restore $CD8^+$ CTL effector functions.[296] Moreover, a robust flux through glycolysis in malignant cells—which at least in some settings results from FTO-dependent epitranscriptomic mechanisms.[297]—has been associated with an increased threshold for TNF sensitivity (see in the following text),[298] as well as to a reduced sensitivity to CTLA4 inhibition.[299]

That said, it has recently been demonstrated that distinct cellular compartment of TME preferentially take up different nutrients, with immune and malignant cells relying on glucose and glutamine as the major fuel source, respectively.[300] Moreover, antagonizing glutamine metabolism has been attributed a cell-specific impact on distinct TME compartments, largely affecting energy metabolism and survival in malignant cells while promoting activation and proliferation of effector T cells, altogether driving robust anticancer immunity.[301] Corroborating the critical role of glutamine metabolism in cancer immune evasion, the cancer cell-specific loss of glutaminase (GLS), a key enzyme for glutamine metabolism, improved effector T cell activation in multiple breast cancer models.[302] Similarly, in a syngeneic model of CRC inhibition of glutamine uptake or metabolism reportedly promoted the expression of Fas cell surface death receptor (FAS) and PD-L1 on the surface of malignant cells, *de facto* favoring their sensitivity to $CD8^+$ CTLs in an ICI-dependent manner.[303] That said, cDC1 functions also depend on glutamine, and, at least in preclinical model of CRC, glutamine supplementation inhibits (rather than boosting) disease progression in the context of restored cDC1 activity.[304]

Taken together, these observations point to glutamine more so than glucose as a potential target for the development of therapeutic strategies to circumvent metabolic coercion. That said, targeted approaches may be required to spare immune effector cells from the detrimental effects of glutamine restriction and hence achieve superior therapeutic activity.

Lactate

Most malignant cells produce abundant lactate levels, largely reflecting their increased uptake of glucose compared to their normal counterparts and/or overexpression of proteins involved in lactate generation or export, namely lactate dehydrogenase A (LDHA).[305] Extracellular lactate favors immunoevasion by promoting the acidification of the TME and by inhibiting the proliferation and function of immune effector cells including $CD8^+$ CTLs and NK cells.[305,306] In melanoma and CRC, lactate as secreted by neoplastic cells exhibiting increased glycolytic flux has been shown to impair the cytotoxicity of $CD8^+$ T cells by a metabolic reprogramming involving reduced pyruvate carboxylase (PC) activity and consequent depletion of tricarboxylic acid (TCA) cycle intermediates.[307] Indeed, melanoma cells often express high LDHA levels and the consequent hypersecretion of lactate has been shown to promote the downregulation of nuclear factor of activated T cells 1 (NFATC1) in $CD8^+$ CTLs and NK cells, leading to decreased synthesis of IFNG and immune escape.[308] Moreover, the loss of *LKB1* is reported to enhance lactate secretion by KRAS-driven lung cancer cells upon the upregulation of lactate transporters such as solute carrier family 16 member 4 (SLC16A4, best known as MCT4), resulting in M2-like TAM repolarization and dysfunctional T cell accumulation.[309] In line with this notion, MCT4 inhibition has been shown to reverse lactate-driven immunosuppression in syngeneic CRC models, *de facto* restoring their sensitivity to ICI-based immunotherapy.[310] Similar results have been obtained in preclinical models of multiple myeloma exposed to pharmacological inhibitors of SLC16A1 (best known MCT1) in combination with CAR T cells.[311]

Supporting its broad immunosuppressive effects, extracellular lactate has also been reported to promote (1) M2-like TAM repolarization in breast cancer and melanoma models, at least in part through the acidification of the TME[312,313] as well as (2) T_{REG} cell functions in various cancers with high glycolytic activity.[314–316] Specifically, lactate appears to boost T_{REG} cell activity not only by providing metabolic support[315] but also by upregulating signal transduction cascades involved in immunosuppression, including TGFB1 and PD-1 signaling.[314,316]

Thus, lactate mediates multipronged immunosuppressive effects either upon uptake by immune cells or via local acidification. Drug development efforts targeting lactate to restore cancer immunosurveillance, though, appear to stand at an impasse.[277]

Other TCA cycle intermediates

Transformed cells often exhibit a considerable rewiring of the TCA cycle, at least in some cases owing to oncogenic mutations in TCA cycle enzymes such as isocitrate dehydrogenase (NADP(+)) 1 (IDH1),[317] which is generally accompanied by the accumulation of immunosuppressive metabolites.[277] For instance, fumarate hydratase (FH) defects lead to an increased secretion of fumarate, which suppresses the cytotoxic activity of tumor infiltrating $CD8^+$ CTLs by promoting the inhibitory succination of zeta chain of T cell receptor associated protein kinase 70 (ZAP70).[318,319] Accordingly, fumarate depletion has been shown to potentiate the efficacy of CD19-targeting CAR T cells in preclinical models of lymphoma.[319] Apparently at odds with these observations, the loss of FH in the healthy kidney reportedly results in intracellular fumarate accumulation and increased immunogenicity via a mechanism that involves the vesicular release of mtDNA and consequent activation of CGAS-STING signaling.[318] Given that *FH* mutations predispose for RCC,[320] it is tempting to speculate that an early and indolent inflammatory response as driven by the loss of FH in healthy cells of the renal epithelium may initiate an oncogenic program that at some stage would also benefit from the fumarate-dependent inhibition of immune effector functions. This possibility remains to be experimentally validated.

The inhibition of acetyl-CoA synthetase 2 (ACSS2) in breast cancer cells results in the microenvironmental accumulation of acetate, which intratumoral $CD8^+$ CTLs have been shown to utilize in support of proliferation and effector functions.[321] Accordingly, pharmacological ACSS2 inhibitors reportedly synergize with immunogenic chemotherapy in preclinical breast cancer models.[321] Gain-of-function mutations in *IDH1* drive the accumulation of *D*-2-hydroxyglutarate (*D*-2HG), a byproduct of the TCA cycle that acts as an oncometabolite by inhibiting various epigenetic regulators that depend on α-ketoglutarate, including DNA demethylases of the TET family.[322] Studies in CRC and melanoma have revealed that tumor-derived *D*-2HG exerts immunosuppressive functions by inhibiting LDHA and glycolysis in $CD8^+$ CTLs, resulting in decreased IFNG signaling and compromised antitumor immunity.[323] Of note, *L*-2HG (which is not produced

by mutant IDH1 but accumulates in response to hypoxia via a promiscuous LDHA activity) also appears to mediate oncogenic effects, at least in the renal setting,[324] and to promote immunoevasion in preclinical PDAC models, although the underlying mechanisms remain to be explored.[325]

These observations are aligned with the notion that oncogenic events, including tumor-promoting alterations of intermediate metabolism, do not only provide cancer cells with a growth advantage but also render them immunoevasive.

Ketone bodies

Human CRCs often exhibit reduced ketogenesis, which is the biochemical pathway through which cells produce alternative fuel sources (ketone bodies) in the absence of sufficient carbohydrate supplies.[326] In this context, a limited metabolic flux though ketogenesis has been associated with the release of CXCL12 from CAFs via a KLF transcription factor 5 (KLF5)-dependent mechanisms, resulting in the recruitment of M2-like TAMs, MDSCs, and T_{REG} cells to the TME and accelerated disease progression.[327] Accordingly, subjecting CRC-bearing immunocompetent mice to a ketogenic diet (i.e., a high-fat and low-carbohydrate dietary regimen), administering them with the ketone body β-hydroxybutyrate or genetically, and promoting ketogenesis upon the overexpression of 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2) in malignant cells have all been reported to restore immunosurveillance and elevate ICI sensitivity.[327] Similar results have recently been obtained in syngeneic models of prostate cancer.[328]

These observations suggest that dietary interventions such as ketogenic diets may constitute promising tools to circumvent metabolic coercion in at least some tumor types.

Methionine and serine

Cancer cells can evade immunity by overconsuming methionine upon the upregulation of the methionine transporter solute carrier family 43 member 2 (SLC43A2, best known as LAT4), thus restricting the availability of this essential amino acid for immune cells.[329] Decreased methionine availability in T cells results indeed in reduced levels of *S*-adenosylmethionine (SAM, a donor of methyl groups for DNA and histone methyltransferases), culminating with the epigenetic repression of genes critically involved in effector functions such as *STAT5*.[329] Apparently at odds with the aforementioned, the accumulation of SAM and other methionine metabolism byproducts such as 5-methylthioadenosine (MTA) has also been reported to mediate immunosuppressive effects by favoring T cell exhaustion (Box 2), at least in preclinical models of HCC and melanoma.[330,331] Interestingly, such an accumulation may emerge from the hyperactivation of methionine adenosyltransferase 2A (MAT2A), which produces SAM, as well as from defects in methylthioadenosine phosphorylase (MTAP), which catabolizes MTA,[330,331] perhaps offering novel targets to circumvent the metabolic coercion of anticancer immunity in these oncological settings.

Methionine restriction has also been shown to promote CGAS activation by interfering with its inactivating methylation by SUV39H1.[170] Similar results have been reported in CRC cells deprived of both endogenous and exogenous sources of the non-essential amino acid serine, resulting in restored sensitivity to ICIs.[182] In this latter scenario, though, CGAS activation appears to be largely driven by the ability of serine restriction to compromise the mitochondrial checkpoint (mentioned previously), resulting in the MOMP-dependent accumulation of interferogenic mtDNA in the cytosol of malignant cells.[182,332]

These observations exemplify the ability of transformed cells to coerce immune effector cells via metabolic pathways stemming from both essential and non-essential amino acids.

Lipids

Neoplastic cells exhibit a major rewiring of lipid metabolism in support of accelerated proliferation,[333] which—at least in some tumors—also promotes immunoevasion. The accumulation of lipids in ovarian cancer cells as driven by the upregulation of fatty acid synthase (FASN) has been shown to impair the cross-priming activity of tumor-infiltrating DCs.[334] Accordingly, FASN inhibition partially restores DC functionality in this setting, leading to improved immunological disease control.[334] Moreover, enhanced fatty acid catabolism in GBM cells as caused by an increased flux of lipid through fatty acid oxidation (FAO) leads to radioresistance and immunoevasion by promoting the upregulation of CD47 (see above).[156] However, whether this mechanism of immuno evasion stems from the accumulation of TCA cycle intermediate with immunosuppressive effects (mentioned previously) has not been formally investigated. Deregulated lipid metabolism also seems to drive immune evasion in the CSC compartment. Specifically, in preclinical models of HCC, the ablation of *Arf1*—which encodes a core regulator of fatty acid metabolism[335]—reportedly fosters the immunogenicity of CSCs, leading to increased tumor infiltration by DCs and restored anticancer immunity.[72] At least in part, however, these observations reflect the ability of ARF1 to preserve the mitochondrial checkpoint and inhibit ISR signaling (mentioned previously).[72]

A major player in immunosuppression as driven by deregulated lipid metabolism in cancer cells is CD36, a broadly expressed long-chain fatty acid transporter.[336] Indeed, CD36 is upregulated by both $CD8^+$ CTLs and T_{REG} cells exposed to fatty acid accumulation in the TME but mediates diametrically divergent effects on these immune cells. On the one hand, $CD8^+$ CTLs respond to CD36-dependent fatty acid uptake by experiencing widespread oxidative stress coupled with the impaired secretion of effector molecular such as IFNG, TNF, and perforin 1 (PRF1).[337,338] On the other hand, CD36 favors the metabolic adaptation of intratumoral T_{REG} cells to a lactate-enriched microenvironment, *de facto* promoting their immunosuppressive functions.[339] In line with this notion, the T_{REG} cell-specific ablation of *Cd36* has been shown to restore immunosurveillance and ICI sensitivity in a syngeneic mouse model of melanoma.[339]

While targeting lipid metabolism to counteract coercion may pose obstacles, notably specificity, these observations point to microenvironmental fatty acids as to potent immunosuppressive factors.

Bioactive lipids

Cancer cells can evade immunity by releasing bioactive lipids into the TME, including PGE_2 and lysoglycerophospholipids. PGE_2—which derives from the sequential catalysis of membrane-released arachidonic acid by prostaglandin-endoperoxide synthase 2 (PTGS2, best now as COX2) and prostaglandin E synthase 2 (PTGES2)[277]—is involved in metabolic coercion in variety of tumors.[340–345]

In some of these settings, increased PGE_2 signaling via prostaglandin E receptor 2 (PTGER2) and/or PTGER4 has been

shown to reduce the functionality of intratumoral cDC1s in support of immune evasion.[340–342] Specifically, PGE_2 has been reported to (1) promote the downregulation of IRF8 and hence reprograms cDC1s toward a dysfunctional state[340]; (2) limit CXCL9 release by cDC1s, hence impeding intratumoral $CD8^+$ CTL differentiation and expansion[342]; and (3) indirectly compromise cDC1 recruitment and activation by limiting NK cell survival, resulting in the suppressed release of the cDC1 chemoattractants CCL5 and X-C motif chemokine ligand 1 (XCL1).[345]

Recently, it has also been shown that PGE_2 promotes immune escape by directly affecting the function and survival of tumor-infiltrating $CD8^+$ CTLs.[343,344] In this setting, PGE_2 signaling via PTGER2 and PTGER4 not only impairs IL2 sensing by $CD8^+$ CTLs, hence limiting their expansion and effector differentiation of $CD8^+$ CTLs[343] but also exposes them to widespread oxidative stress coupled with ferroptotic cell death.[344] Finally, PGE_2 has been reported to favor immunoescape during pancreatic tumorigenesis by driving the differentiation of tumor-infiltrating monocytes into M2-like TAMs.[346]

LPC does not only mediate immunosuppressive effects by promoting the silent efferocytic removal of dying cells and their corpses by macrophages (mentioned previously)[97] but also as a substrate for the ENPP2-mediated synthesis of lysophosphatidic acid (LPA).[347] ENPP2 is overexpressed in some malignancies including ovarian cancer, promoting the LPA-driven release of PGE_2 from DCs and the consequent autocrine and paracrine suppression of anticancer immunity.[347]

These few observations exemplify the multipronged immunosuppressive effects enabled by the LPC-LPA-PGE_2 axis. While this axis can be efficiently targeted by a number of clinically available COX2 inhibitors (e.g., celecoxib and aspirin), past efforts to combine COX2 blockers with chemotherapy or radiotherapy have generally failed to demonstrate a superiority for the combinatorial regimen over standard-of-care (SOC).[348]

Vitamins and retinoic acid

Vitamins and their derivatives can modulate anticancer immunity by affecting various immune effector cells. For instance, pancreatic cancer cells restrict vitamin B_6 availability to NK cells, which require this metabolite for activation, at least in part by regulating glycogen metabolism.[349] Similar results have been obtained with the vitamin B_3 precursors nicotinamide (NAM), at least in preclinical models of mammary carcinoma and PDAC.[350–352] In line with these observations, vitamin B_6 or NAM supplementation has been shown to promote NK cell functions, both in syngeneic PDAC models[349] or in *ex vivo* settings prior to ACT.[353] Conversely, sarcoma cells reportedly coerce immune effectors by overproducing retinoic acid (RA).[354] RA appears to inhibit the transcriptional activity of IRF4 in intratumoral monocytes, thus promoting the accumulation of immunosuppressive TAMs over DCs.[354]

In summary, at least some cancer types alter the local abundance of vitamins and their precursors in support of immunosuppression. While some attempts at utilizing specific vitamins, notably vitamin C, as anticancer agents in the clinic are underway,[355] most of them were developed in an immune-agnostic manner.

Potassium

Ion channels, and in particular potassium channels, regulate T cell functionality.[356] Accordingly, elevated concentrations of extracellular potassium as released by dying melanoma cells have been shown to compromise the functionality of intratumoral $CD8^+$ CTLs by suppressing mTORC1 signaling.[357] Moreover, increased environmental levels of potassium have been reported to inhibit nutrient uptake by effector T cells, resulting in the activation of an autophagic response coupled with decreased availability of histone acetylation donors (e.g., acetyl-CoA) and consequent downregulation of effector molecules.[358] At least in preclinical models of melanoma, such an ionic coercion has been associated with decreased tumor control by adoptively transferred $CD8^+$ CTLs.[358]

These observations indicate that the ionic balance of the TME is important for immunosurveillance, opening the possibility to genetically engineer (CAR) T cells prior to infusion to circumvent ionic coercion. To the best of our knowledge, this possibility is not being explored.

CYTOPROTECTION

Both $CD8^+$ CTLs and NK cells kill malignant cells upon the establishment of the so-called ‘‘immunological synapse’’, a highly organized structure that physically connects immune effector cells with their targets and enables the polarized (1) release of cytotoxic molecules including GZMB and PRF1; (2) expression of death receptor ligands, such as Fas ligand (FASLG); and (3) release of tumor-targeting cytokines, notably IFNG.[359] Neoplastic cells can evade immune elimination by effector cells that normally recognize them as transformed and hence normally engage in cytotoxic and secretory functions though a variety of cytoprotective mechanisms that either involve defects in the formation of the immunological synapse or the activation of cell death pathways downstream thereof, or rely on the initiation of compensatory responses such as autophagy (Figure 4).

Alterations of the immunological synapse

At least in some cases, cancer cells evade immune cytotoxicity via mechanical properties that result in decreased sensitivity to GZMB and PRF1. For instance, TRCs appear to evade immune attack due to their unique cellular softness as compared to their more differentiated counterparts, resulting in insufficient contractile force for PRF1 pore formation at the immunological synapse, at least in preclinical melanoma and breast cancer models.[360] Similar findings have been documented in models of T cell leukemia, at least in part emerging from the downregulation of the cytoskeletal component filamin A (FLNA), a process that also appears to protect CTL themselves from PRF1-mediated lysis.[361] Moreover, breast cancer cells resisting NK cell killing appear to display extensive actin remodeling at the immunologic synapse, resulting in decreased access of GZMB to the cytosol and hence robust cytoprotection.[362] Finally, it has been shown that insufficient target cell contraction (which is mediated by the actin cytoskeleton) prevents the rapid dissolution of the immunological synapse, resulting in effector cell retention and limited engagement of additional targets.[363]

Along similar lines, malignant cells can actively compensate for PRF1 and GZMB killing at the immunological synapse. For instance, melanoma cells have been shown to react to the formation of the immunological synapse with an increased

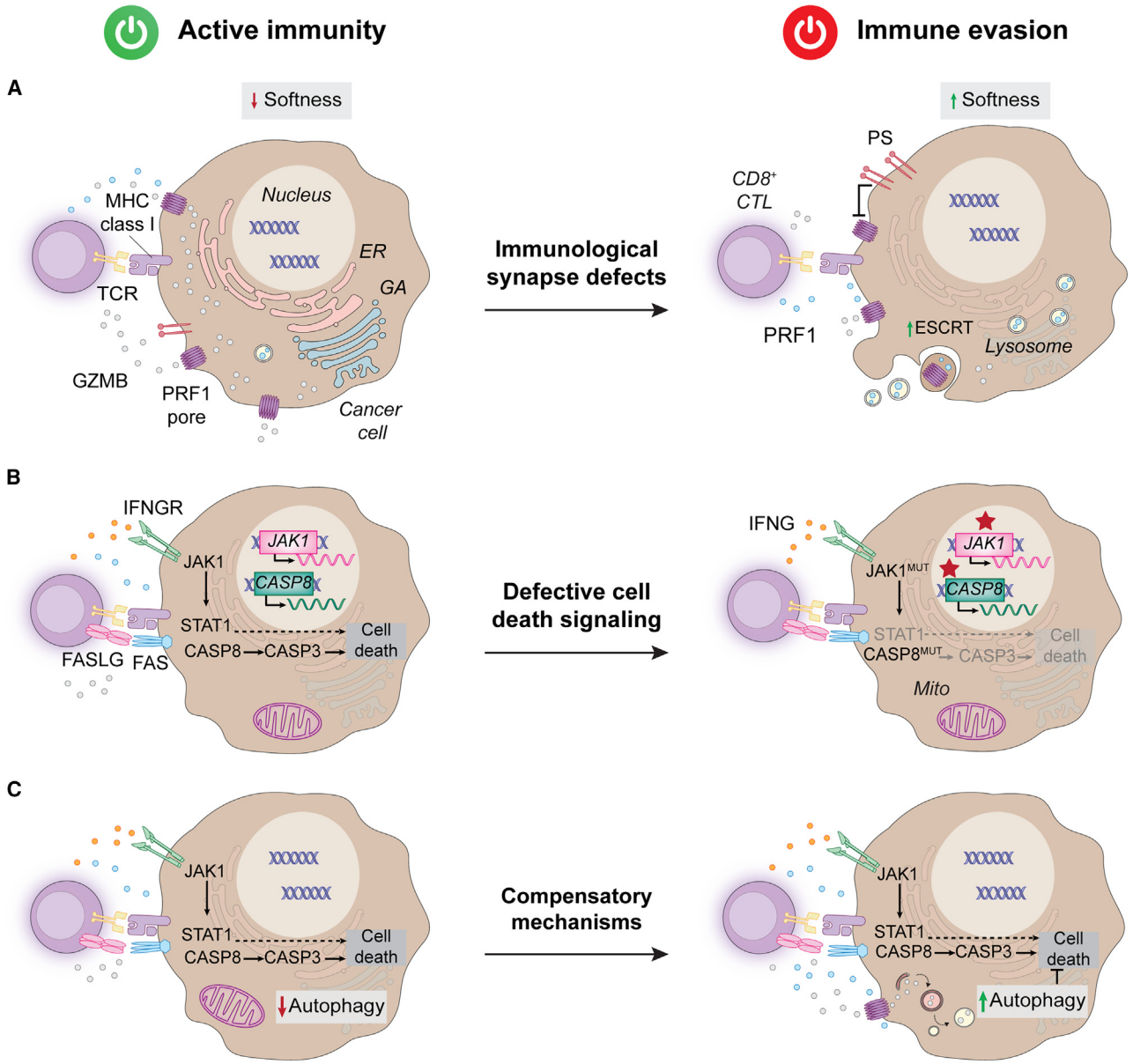

Figure 4. Cytoprotection in cancer immune evasion

Cancer cells of different histology can evade tumor-targeting immune responses by acquiring an increased resistance to immune effector molecules such as perforin 1 (PRF1), granzyme B (GZMB), tumor necrosis factor (TNF), or interferon gamma (IFNG). Such a decreased sensitivity to cytolysis by immune effector cells can involve (1) mechanical defects of the immune synapse, generally resulting in inhibited PRF1-mediated pore formation or improved endosomal sorting complexes required for transport (ESCRT)-dependent membrane repair (A): (2) defects in Fas cell surface death receptor (FAS) and IFNG signal transduction, at least in some cases linked to caspase 8 (*CASP8*) and Janus kinase 1 (*JAK1*) mutations (B); and (3) the activation of compensatory cytoprotective pathways including (but not limited to) autophagy (C). CASP, caspase; $CASP8^{MUT}$, mutant caspase 8; CTL, cytotoxic T lymphocyte; ER, endoplasmic reticulum; FASLG, Fas ligand; GA, Golgi apparatus; GZMB, granzyme B; $JAK1^{MUT}$, mutant Janus kinase 1; PRF1, perforin 1; PS, phosphatidylserine; STAT1, signal transducer and activator of transcription 1; TCR, T cell receptor.

vesicular trafficking and secretion, resulting in degradation of PRF1 by lysosomal cathepsins and cytoprotection.[364] Moreover, both melanoma and CRC cells have been reported to harness endosomal sorting complexes required for transport (ESCRT) factors at the immunological synapse to actively repair PRF1 pores and consequently limit cytosolic GZMB entry.[365] Moreover, irradiated cancer cells appear to acquire transient resistance to NK cell killing by a mechanism involving PRF1 inhibition by surface-exposed PS.[366]

Altogether, these observations exemplify mechanical and biological processes through which malignant cells achieve cytoprotection from immune effector cells. Pharmacological inhibitors of these mechanisms may result in superior cancer cell elimination by $CD8^+$ CTLs and NK cells and hence superior ICI

sensitivity across a variety of neoplasms, a possibility that has just began to be explored.

Defective cell death signaling

Genomic studies on biopsies from patients with solid tumors have revealed frequent mutations in *CASP8*,[24] which encodes for an apoptotic caspase activated by FAS.[227] In line with this notion, malignant cells have been shown to frequently downregulate FAS by epigenetic mechanisms, resulting in accrued resistance to NK cell cytotoxicity.[367] Similar observations have been made in preclinical models of CRC and lung carcinoma, although in this setting glutamine metabolism appeared to suppress FAS expression.[303] Moreover, the sensitivity of melanoma and CRC cells to immune effectors including $CD8^+$ CTLs and NK cells appears to rely on intact TNF signaling, as demonstrated by a CRISPR screen that identified multiple TNF signal transducers involved in cytotoxicity.[368] Similar observations have been made in syngeneic PDAC models, although in this setting decreased TNF sensitivity appeared to emerge from the EMT-driven repression of IRF6.[369] Melanoma cells also display frequent genetic defects in IFNG signal transducers, resulting in limited activation of JAK-STAT signaling and consequent cytoprotection from IFNG-mediated killing.[370] Along similar lines, SRY-box transcription factor 17 (SOX17) overexpression has recently been shown to increase the resistance of CRC cells to IFNG,[371] although the precise mechanisms underlying this observation remains to be characterized.

Corroborating the importance of operational cell death signaling in cancer cells for efficient immunosurveillance, defects in TNF and IFNG signaling have been consistently associated with resistance to immunotherapy. For instance, ICI-unresponsive tumors have been reported to display an increased cytotoxicity threshold to effector cytokines including TNF.[372,373] In line with this notion, lowering the threshold for efficient TNF signaling in melanoma cells by TNF receptor associated factor 2 (*Traf2*) ablation or pharmacological inhibition of TBK1 has been shown to restore ICI sensitivity by a mechanism involving the induction of receptor interacting serine/threonine kinase 1 (RIPK1)- and caspase-dependent cancer cell death.[372,373] Similar observations linking lowered TNF signaling threshold to improved disease control and restored ICI sensitivity have been made in preclinical models of highly glycolytic lung and pancreatic cancer subjected to the depletion of solute carrier family 2 member 1 (SLC2A1, a glucose transporter best known as GLUT1) (mentioned previously).[298] Finally, a rewiring of IFNG signaling from STAT1 activation to the upregulation of the endogenous cell cycle inhibitor cyclin dependent kinase inhibitor 1B (CDKN1B, best known as $p27^{KIP1}$) and consequent acquisition of a dormant state has been linked with IFNG resistance in melanoma-repopulating cells.[288]

Corroborating the key role of cell death defects in immune evasion, in patients with refractory/relapsed B-cell non-Hodgkin lymphoma, resistance to CD19-targeting CAR T cells has been associated with BCL2 amplifications.[374] Accordingly, the FDA-approved BCL2 inhibitor venetoclax has been shown to sensitize CAR T cell-refractory lymphoma cells to therapy.[374] Of note, IFNG has recently been reported to promote ferroptotic lipid oxidation in malignant cells, by a dual mechanism involving (1) downregulation of solute carrier family 3 member 2 (SLC3A2) and solute carrier family 7 member 11 (SLC7A11) and consequent decrease of intracellular cysteine (which mediates robust antioxidative effects); and/or (2) activation of acyl-CoA synthetase long chain family member 4 (ACSL4) and consequent reprogramming in lipid metabolism.[375,376] Of note, at least in some malignant cells, GZMB has also been shown to promote a gasdermin E (GSDME)-dependent regulated variant of necrosis commonly known as pyroptosis.[377] Whether malignant cells can harness CASP7 and sphingomyelin phosphodiesterase 1 (SMPD1) to repair PRF1 and GSDME pores as demonstrated in preclinical models of bacterial infection,[378] however, remains to be clarified.

Collectively, these observations indicate that cytoprotection as a consequence of common defects in cell death signal transduction is beneficial to malignant cells not only by virtue of an increased resistance to stress, but also because of immunoevasion.

Compensatory mechanisms

Malignant cells can activate a number of cell-wide pathways that protect them from the cytotoxicity of immune effectors. For instance, multiple tumor types have been shown to respond to $CD8^+$ CTL activation by overexpressing SERPINB9,[379,380] which is generally harnessed by immune effectors themselves including $CD8^+$ CTLs and DCs to avoid GZMB cytotoxicity.[381,382] Especially under hypoxic conditions (Box 1), cancer cells of different histological derivation can also achieve increased resistance to immune effector molecules including IFNG, TNF, and GZMB upon activation of autophagy,[383] via a mechanism that appears to involve the activating phosphorylation of STAT3,[384] as well as lysosomal GZMB degradation.[385]

That said, autophagy in malignant cells is critically involved in the ICD-associated release of ATP (mentioned previously), and immune effector cells have been shown to kill their malignant counterparts in an immunogenic manner.[386,387] Moreover, autophagy has been reported to promote the degradation of tenascin C (TNC)—an extracellular matrix glycoprotein contributing to immune evasion—in preclinical TNBC models, *de facto* favoring tumor-targeting immune responses.[388] Thus, at least hypothetically, autophagic defects may results in the inhibition of CTL cytotoxicity and the ATP-dependent feedforward amplificatory loops it may elicit.

In summary, various compensatory mechanisms can be utilized by transformed cells to resist killing by TNF, IFNG, and the PRF1-GZMB system.

Other mechanisms

TFGB1 has also been reported to promote cytoprotection by limiting the sensitivity of malignant cells to $CD8^+$ CTLs, via a mechanism involving SOX4.[389] While the precise link between SOX4 expression and the increased resistance of cancer cells to lysis by $CD8^+$ CTLs remains to be formally established, SOX17 has also been shown to provide CRC cells with cytoprotection, at least in part reflecting decreased sensitivity to IFNG (mentioned previously),[371] potentially suggesting the implication of a similar mechanism. An accrued resistance to immune cytotoxicity has also been associated with the acquisition of a quiescence phenotype characterized by transcriptional features of hypoxic responses by transformed cells,[115] but the molecular

underpinnings of this process have not yet been thoroughly dissected.

NOVEL PHARMACOLOGICAL STRATEGIES TO TARGET IMMUNE EVASION IN THE CLINIC

Over the past two decades, multiple clinically relevant pharmacological strategies have been conceived to target camouflage, coercion and cytoprotection, and some of these *bona fide* immunotherapies have already entered routine clinical use. The latter include (1) a number of ICIs targeting PD-1, PD-L1, CTLA4, or LAG3, which operate by inhibiting coercion as driven by co-inhibitory ligands expressed by cancer cells[390]; (2) CAR T cells and bispecific antibodies, which circumvent camouflage[391,392]; and (3) some recombinant cytokines and TLR agonists,[393] which operate by targeting coercion as driven by immunosuppressive shifts in cytokine and DAMP signaling. Moreover, a number of FDA approved anticancer treatments that have been developed in an immune agnostic manner have been found to inhibit immune evasion (by a multitude of mechanisms), *de facto* promoting the (re)instatement of tumor-targeting immunity. These include (1) some cytotoxicants such as anthracyclines and oxaliplatin[12]; (2) some targeted anticancer agents encompassing a variety of tyrosine kinase inhibitors (TKIs), tumor-targeting antibodies, epigenetic modifiers and the BCL2 inhibitor venetoclax[13]; and (3) at least in some settings, focal radiotherapy.[14]

Besides these established approaches, numerous clinical trials—including a few phase III studies (Table 1)—are now open to investigate hitherto experimental strategies to inhibit immune evasion, which generally aim at (1) inhibiting coercion by co-inhibitory ligands; (2) inhibiting metabolic coercion and suppressed cytokine signaling; or (3) simultaneously targeting multiple "Cs".

Inhibiting coercion by co-inhibitory ligands

Considerable attention is being devoted to blocking the coercive effects of co-inhibitory receptors other than PD-1, CTLA4, and LAG3, notably TIM-3, TIGIT, VISTA, and NKG2A, generally in combination with FDA-approved PD-1 or PD-L1 blockers.[284] Combinations of this type that are currently being investigated in clinical trials enrolling patients with advanced solid tumors (unless specified) include (1) pembrolizumab plus the VISTA inhibitor KVA12123[394]; (2) the PD-1 blocker dostarlimab plus the TIM-3 inhibitor TSR-022,[395] or the TIGIT inhibitor EOS-448[396] (in patients with lung cancer); (3) the PD-1 inhibitor nivolumab plus the TIGIT-targeting antibodies BMS-986207[397] or etigilimab (both in patients with ovarian carcinoma); (4) the PD-1 blocker tislelizumab plus the anti-TIGIT monoclonal antibody ociperlimab[398] (in subjects with lung cancer, biliary tract carcinoma, or lymphoma); (5) the PD-1 blocker toripalimab plus the TIGIT blocker JS006; and (6) the PD-L1 inhibitor avelumab plus the TIGIT-targeting agent M6223[399] (in individuals with urothelial carcinoma). Along similar lines, the NKG2A blocker monalizumab[145] with or without SOC chemotherapy is being investigated in combination with the FDA-approved PD-L1 inhibitor durvalumab (in patients with lung cancer or head and neck carcinoma), optionally along with the experimental CD73 inhibitor oleclumab[400] (in subjects with lung cancer), as well as with the dual CTLA4 and PD-1 blocker MEDI5752[401] (in individuals with CRC). Finally, two dual TIGIT and PD-L1 inhibitors, namely HB0036[402] and HLX301,[403] are currently being tested in patients with advanced solid tumors as standalone therapeutic agents (source www.clinicaltrials.gov).

Two CD47 blockers are currently being investigated in clinical trials: (1) magrolimab[404] is being tested—invariably along with SOC chemotherapy and/or one or more ICI(s)—in multiple cohorts of patients with solid and hematological malignancies; and (2) lemzoparlimab,[405] which is being tested for safety and efficacy in combination with azacytidine in individuals with myelodysplastic syndromes (MDSs). Finally, a number of SIRPA-Fc fusion proteins are under clinical evaluation, including (1) TTI-622,[406] which is being tested along with pembrolizumab in patients with lymphoma; (2) evorpacept,[407] which is being investigated as a combinatorial partner for venetoclax and azacytidine in patients with hematological malignancies, or for ICIs in subjects with CRC and gastric cancer; and (3) IMM001, whose safety and efficacy are being assessed in combination with tislelizumab in patients with Hodgkin's lymphoma, or with azacitidine in individuals with AML and MDS (source www.clinicaltrials.gov).

Collectively, these studies testify the considerable interest raised among clinical and pharmaceutical companies by the possibility to effectively target the immunosuppressive pathways elicited by co-inhibitory receptors other than PD-1, CTLA4, and LAG3 and anti-phagocytic receptors.

Inhibiting metabolic coercion and suppressed cytokine signaling

An attractive area of clinical investigation is focusing on agents that target coercion as driven by metabolic cancer cell rewiring.[277] For instance, the glutamine antagonist DRP-104[408] is being explored in combination with durvalumab in patients with fibrolamellar carcinoma. The safety and efficacy of the MCT1 inhibitor AZD3965[409] optionally combined with the FDA approved CD20-targeting agent rituximab are currently being evaluated in individuals with B-cell malignancies and advanced solid tumors. Restoring methionine metabolism in $CD8^+$ CTL_S via SAM administration along with PD-1 inhibition and optional VEGF signaling blockage is also under clinical evaluation in patients with HCC or RCC. The FASN inhibitor TVB-2640 is being assessed as standalone therapeutic intervention or combined with endocrine therapy in patients with CRC as well as prostate and breast cancer. Finally, while the ADORA2A antagonists ciforadenant[410] and inupadenant are being tested in combination with ICIs or chemotherapy in individuals with solid tumors, including NSCLC and RCC, the dual ADORA2A and ADORA2B blocker etrumadenant[411] is being assessed combined with immunotherapy, chemotherapy, and/or radiotherapy in subjects solid tumors including NSCLC, prostate cancer, and CRC (source www.clinicaltrials.gov).

Considerable attention also remains around the possibility to boost immunostimulatory cytokine signaling via DDR inhibitors and pattern recognition receptor (PRR) agonists, notably STING agonists.[412] In line with this notion, a number of ATR inhibitors including (but not limited to) ceralasertib,[413] berzosertib,[414] and camonsertib,[415] as well as the WEE1 G2 checkpoint kinase (WEE1) inhibitor adavosertib[416] are currently being investigated as monotherapies or combined with ICIs across various oncological indications. Similar considerations apply to inhibitors of ATR and ATM signal transducers, such as the checkpoint

Table 1. Advanced clinical trials investigating conceptually novel approaches to target cancer immune evasion in patients with cancer

Target[a]	Drug	Indication	Phase	Status	Notes	Reference
ATR	Ceralasertib	Non-small cell lung carcinoma	III	Active, not recruiting	In combination with durvalumab	NCT05450692
CD36 CD47	VT1021	Glioblastoma	II/III	Recruiting	In combination with standard-of-care chemoradiation	NCT03970447
CD47	Evorpacept	Gastric carcinoma	II/III	Recruiting	In combination with multimodal chemoimmunotherapy	NCT05002127
	Lemzoparlimab	Myelodysplastic syndrome	III	Recruiting	In combination with azacytidine	NCT05709093
CD73	Oleclumab	Non-small cell lung carcinoma	III	Recruiting	In combination with durvalumab	NCT05221840
FASN	TVB-2640	Glioblastoma	III	Recruiting	In combination with bevacizumab	NCT05118776
TGFB1 (PD-L1)	Bintrafusp alfa	Non-small cell lung carcinoma	III	Active, not recruiting	As standalone therapeutic agent	NCT05061823

[a]Source: www.clinicaltrials.gov, current as of June 24th, 2024. Restricted to Phase II/III or higher studies with status "Active, not recruiting", "Not yet recruiting" and "Recruiting", and investigating pharmacological agents with no FDA-approved target.

kinase 1 (CHEK1) blocker BBI-355 as well as the CHEK2-targeting agent PHI-101.[417] Moreover, the pharmacological STING activators IMSA101[418] and TAK-676[419] are being tested in combination with personalized ultrafractionated stereotactic adaptive radiation therapy (PULSAR) plus ICIs or pembrolizumab, respectively, in patients with advanced solid tumors (source www.clinicaltrials.gov). That said, STING agonists have previously been shown to exert robust antiproliferative and cytotoxic effects on $CD8^+$ CTLs,[420,421] potentially limiting the therapeutic effects of this approach.

In summary, while some pharmacological inhibitors of metabolic coercion and suppressed cytokine signaling remain under clinical investigation, targeting metabolic and immunomodulatory pathways with systemic interventions has considerable limitations linked to specificity that have not yet been circumvented.[393,422]

Simultaneously targeting multiple "Cs"

A number of novel pharmacological regimens under clinical evaluation simultaneously (at least hypothetically) inhibit different mechanism of immunoevasion, potentially offering clinical advantages in the context of highly heterogeneous tumors that may harness multiple pathways to evade anticancer immunity in different intratumoral areas.[11] As mentioned previously, a number of clinically employed anticancer agents inhibit immune evasion, including a number of drugs like FDA-approved epigenetic modifiers that simultaneously target camouflage and coercion, like azacytidine, decitabine, and multiple HDAC inhibitors.[423] In this context, novel approaches involve PRMT5 inhibitors, which are being investigated mostly as standalone therapeutic agents in early-phase clinical studies enrolling patients with solid tumors deficient for methylthioadenosine phosphorylase (MTAP) or non-Hodgkin's lymphoma, as well as the KDM1A inhibitors bomedemstat and seclidemstat, which are being tested in combination with ICIs in subjects with lung cancer, or with azacytidine in patients with MDS and chronic myelomonocytic leukemia (source www.clinicaltrials.gov). That said, most (if not all) immune cells also rely on epigenetic mechanisms for their survival, proliferation, and effector functions,[423] implying that pharmacological epigenetic modifiers may have unwarranted immunosuppressive effects unless precise targeting strategies are developed.

Additional strategies targeting conceptually distinct mechanisms of immune evasion (notably camouflage and coercion, see aforementioned) include (1) VT1021 (a dual CD36 and CD47 inhibitor, hence targeting both camouflage and coercion)[424] which is being assessed in patients along with SOC temozolomide-based chemoradiation in subjects with GBM; (2) the CD73 antagonists quemliclustat and oleclumab, which are being tested along with ICIs and (at least in some settings) other (immuno)therapeutic agents in patients with a variety of solid tumors; (3) the dual BCL2 and BCL2-like 1 (BCL2L1, best known as BCL-X_L) inhibitors (and hence MOMP inducers) navitoclax and pelcitoclax and R-(−)-gossypol acetic acid (AT-101),[425] which are being investigated as combinatorial partners for SOC chemotherapy and/or immunotherapy most often in patients hematological malignancies; as well as (4) the transforming growth factor β receptor 1 (TGFBR1) inhibitor vactosertib[426] which is being tested along with ICIs in patients with NSCLC, CRC, or gastric cancer, an autologous cancer vaccine encompassing genetic engineering for TGFB1 and TGFB2 inhibition (gemogenovatucel-T) which is being investigated as adjuvant therapy for women with ovarian carcinoma, and the dual TGFB1 and PD-L1 blocker bintrafusp alfa[427] which is being evaluated alone or in combination with additional drugs in patients with solid tumors including NSCLC patients (source www.clinicaltrials.gov). Previously reported clinical studies have shown that blocking TGFB1 is safe and mediates at least some efficacy when combined with SOC therapeutic strategies.[253] Whether this strategy will soon receive regulatory approval for use in humans, however, remains unclear.

Despite this and other unknowns, simultaneously targeting camouflage and coercion stands out as a promising approach to avert immuno evasion in a variety of tumors as it potentially addresses elevated degree of intratumoral heterogeneity that may be associated with the acquisition of different immunoevasive properties by malignant cells in different tumor areas.

CONCLUDING REMARKS

Here, we propose a novel conceptual framework to classify cancer immunoevasion by suggesting that most mechanisms through which malignant cells escape immune recognition and

elimination involve either of "three Cs": camouflage, coercion, or cytoprotection. Such a framework is obviously not devoid of limitations. For instance, some malignant cells exhibit genetic or epigenetic defects that simultaneously engage more than one "C". As a standalone example, EZH2 has been shown to promote both camouflage and coercion, downstream of the epigenetic silencing of MHC class I molecules, STING, and pro-inflammatory cytokines.[30,68,166] Along similar lines, some pathways of immunoevasion are difficult to precisely classify as a single "C" or may be framed as different "Cs" in a context-dependent manner. For instance, whereas accrued ATP degradation may *a priori* underlie both camouflage and coercion,[59] the latter would be the predominant mechanism of immunoevasion in tumors that exhibit robust infiltration by immune effector cells at baseline. Some malignant cells have also been shown to utilize mechanisms of immunoevasion that are difficult to frame within the "three Cs" paradigm. For instance, HCC-infiltrating NK cells appear to exhibit surface defects due to altered sphingomyelin (SM) content that prevent them from recognizing and lysing tumor cells,[428] but (1) the precise molecular mechanisms causing such alterations remain to be determined, and (2) whether this is a form of coercion or cytoprotection is unclear. Along similar lines, disseminated dormant cancer cells appear to be so rare that their likelihood to interact with the host immune system in support of active immunosurveillance is extraordinarily low,[429] a mechanisms of immune evasion that is difficult to reconduct to conventional camouflage, coercion, or cytoprotection. Finally, the loss of the Y chromosome (LOY)—which is frequent across tumor types—has been linked to an increased propensity of host $CD8^+$ CTLs for exhaustion, resulting in immunoevasion and accelerated disease progression by a hitherto poorly defined mechanism.[430]

At least hypothetically, malignant cells evading anticancer immunity through a specific "C" (e.g., camouflage) may not need to acquire additional immunoevasive mechanisms (e.g., coercion or cytoprotection), as *de facto* no longer exposed to a selective immune pressure. While some clinical data in support of this possibility exists,[25,431–434] (1) passenger alterations potentially generating extra immunoevasive phenotypes, as far as non-detrimental for cancer cells, remain possible; and (2) most importantly, as most neoplasms exhibit considerable degree of intratumoral heterogeneity (both across distinct lesions in the same patient, and within a single lesion), it is likely that malignant cells populating different tumor areas may evade immunity by different mechanisms.[11] This implies that, at least in some cases, simultaneously inhibiting distinct mechanisms of immuno evasion may have superior therapeutic effects as compared to targeting only one "C". That said, whether a specific "C" would be hierarchically superior to others (and hence represent a preferential target for therapy) not only remains to be experimentally demonstrated but also may exhibit a considerable degree of context dependency and hence vary in different oncological settings.

Importantly, at least some manifestations of the "three Cs" have been successfully employed to guide clinical decision making in a variety of oncological indications.[435] For instance, an elevated tumor mutational burden (TMB) as assessed on diagnostic biopsies by FDA-approved detection kits are currently being employed to allocate patients with cancer to pembrolizumab irrespective of disease histology.[20] Along similar lines, PD-L1 expression levels on malignant and/or immune cells are routinely employed to direct the use of PD-1 or PD-L1 blockers in numerous oncological settings.[436] That said, a fraction of PD-L1-positive tumors fails to respond to ICI as standalone therapeutics,[436] which (1) potentially points to the existence of PD-L1-independent mechanisms of immunoevasion, and (2) calls for the identification of complementary (if not alternative) predictive biomarkers of response. In this setting, an expanding clinical literature suggests that assessing the proficiency of IFNG signaling in malignant cells may convey additional predictive information as compared to the quantification of PD-L1 expression alone.[314,370,437,438] Whether diagnostic tests assessing IFNG signaling in malignant cells as a predictor of ICI sensitivity will soon enter the clinical routine, however, is unclear.

Despite these and other unknowns, we believe that the "three Cs" framework proposed herein may facilitate the understanding of a complex phenomenon such as immune evasion, and potentially guide the discovery of novel, clinically relevant strategies to circumvent it.

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AUTHOR CONTRIBUTIONS

L.G. conceived the article. C.G., I.V., and L.G. wrote the first version of the manuscript with critical input from T.A.C. C.G. designed display items under supervision from L.G. All authors approve the submitted version of the article.

DECLARATION OF INTERESTS

T.A.C. is a co-founder of Gritstone Oncology and holds equity in Gritstone Oncology and An2H, is/has been holding research contracts with Bristol-Myers Squibb, AstraZeneca, Illumina, Pfizer, An2H, and Eisai, has served as an advisor for Bristol-Myers, MedImmune, Squibb, Illumina, Eisai, AstraZeneca, and An2H, and is an inventor on intellectual property and a patent held by MSKCC on using tumor mutation burden to predict immunotherapy response, which has been licensed to PGDx. L.G. is/has been holding research contracts with Lytix Biopharma, Promontory, and Onxeo, has received consulting/advisory honoraria from Boehringer Ingelheim, AstraZeneca, AbbVie, OmniSEQ, Onxeo, The Longevity Labs, Inzen, Imvax,

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