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REVIEW

Mechanisms regulating immune surveillance of cellular stress in cancer

Ruth Seelige[1] · Stephen Searles[1] · Jack D. Bui[1]

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Abstract The purpose of this review is to explore immune-mediated mechanisms of stress surveillance in cancer, with particular emphasis on the idea that all cancers have classical hallmarks (Hanahan and Weinberg in Cell 100:57–70, 67; Cell 144:646–674, 68) that could be interrelated. We postulate that hallmarks of cancer associated with cellular stress pathways (Luo et al. in Cell 136:823–837, 101) including oxidative stress, proteotoxic stress, mitotic stress, DNA damage, and metabolic stress could define and modulate the inflammatory component of cancer. As such, the overarching goal of this review is to define the types of cellular stress that cancer cells undergo, and then to explore mechanisms by which immune cells recognize, respond to, and are affected by each stress response.

Keywords Cancer immune surveillance · Cancer immunity · Cancer-associated stress · Cancer inflammation · Tumor microenvironment · ER stress · Unfolded protein response · Immunogenic cell death · Danger-associated molecular patterns (DAMPs) · Chromosome instability (CIN) · Hyperploidy · Senescence-associated secretory phenotype (SASP) · DNA damage response (DDR) · Oncometabolites · Mitochondrial stress

Introduction

Almost all tumors have an inflammatory component that contributes a significant portion of the cellularity to the growing mass. This inflammatory component consists of resident and/or infiltrating immune cells and has been categorized as a bonafide "hallmark" of cancer [68]. The activity of these immune cells can either promote cancer growth, e.g., "cancer related inflammation" or inhibit cancer progression, e.g., "cancer immune surveillance". Given these disparate activities of immunity on cancer progression, it is important to understand the characteristics of cancer cells that regulate the inflammatory constituents that inhabit almost all cancers. Indeed, the field of cancer immune therapy, heralded as a "Breakthrough of the Year" [33], critically relies on mobilizing anti-tumor immune effectors while diminishing the activity of pro-tumor inflammation. In this review, we provide a summary of how intrinsic cellular stress modulates immune cell infiltration or activity. We focus on oxidative stress, proteotoxic stress, mitotic stress, DNA damage and metabolic stress as key cancer intrinsic hallmarks [101] that can impact on cancer's extrinsic hallmark of immunity and inflammation. Figure 1 shows that the stresses that cancer cells experience and sense can result in both pro- or anti-tumor outcomes. All of these stress pathways are closely interrelated and can directly cause or be caused by one another (Fig. 2). This review focuses largely on the downstream effects of these five stressors, and we acknowledge that the transformed state, chemotherapies, and radiotherapies all can induce some form of cellular stress.

Ruth Seelige and Stephen Searles contributed equally.

✉ Jack D. Bui
jbui@ucsd.edu

[1] Department of Pathology, University of California, 9500 Gilman Dr MC 0612, La Jolla, CA 92093-0612, USA

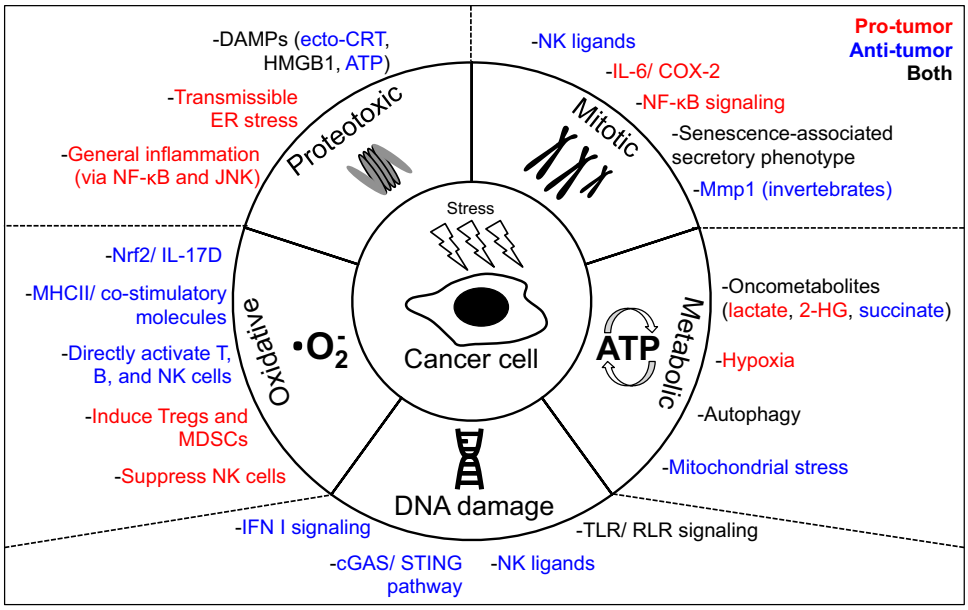

Fig. 1 Regulation of immune surveillance by intrinsic stress pathways in cancer. Shown are the five unique stress pathways that occur in cancer cells (*inner circle*) and the effects of each stress on immunity (*outer circle*). These effects are broad reaching and can promote (*red font*) and/or inhibit (*blue font*) anti-tumor immunity, or both (*black font*). Adapted from Luo et al. [101]

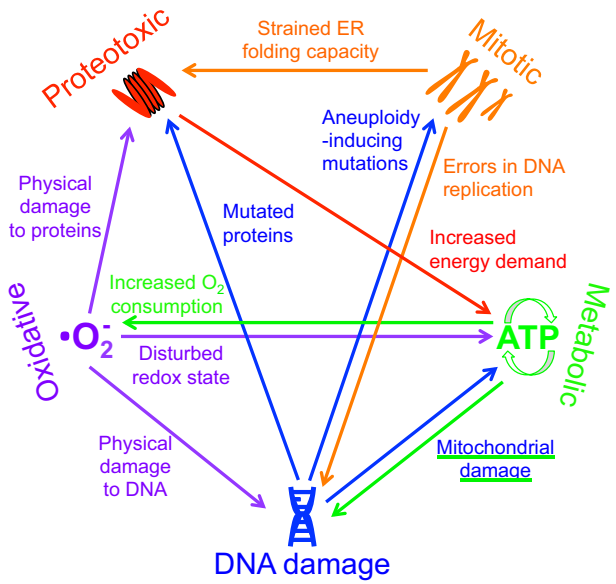

Fig. 2 Interrelation of stress pathways. The five stress pathways that occur in cancer cells are highly interrelated and can each directly cause at least one or more other stress response. The *arrows* demonstrate direct (rather than indirect) interconnections between each of the five stress pathways, and the *text next to each arrow* describes how each direct effect is mediated

Oxidative stress

Oxidative stress occurs in cancer when the balance between reactive oxygen species (ROS) and the ability of the cell and its microenvironment to detoxify them is disturbed, resulting in the accumulation of free oxygen radicals such as hydrogen peroxide (H_2O_2), the superoxide radical (O_2^-) or the hydroxyl radical (OH). Due to the toxic effects of ROS on different components of a cell, oxidative stress is closely related to each of the other four forms of stress discussed in this review (DNA damage, proteotoxic, mitotic, and metabolic). For example, it can directly cause DNA and protein damage or cause and be caused by metabolic stress (Fig. 2). On the other hand, ROS are important second messengers during cell signaling and homeostasis, and a tightly regulated balance of their production and their scavenging is needed for transformation-free cell survival.

Because of ROS' cytotoxic and DNA-damaging effects, they are closely associated with tumorigenesis, which has been reviewed elsewhere [129, 148, 149]. However, the overall impact of ROS on cancer progression is difficult to predict, as ROS can exert both pro- and anti-tumor effects. Moreover, ROS also impact positively and negatively on immune function, and thus can indirectly affect cancer progression via their control of cancer immune surveillance. In this section, we focus on the impact of ROS on immune cells and will interpret these effects in the context of cancer progression.

Although ROS are abundant in the tumor microenvironment, their origin has not been completely dissected. Phagocytes such as neutrophils and macrophages are a major source of ROS, but excessive ROS production by tumor cells has also been widely accepted and may even be regarded as a hallmark of cancer [129]. ROS from tumor cells can influence the immune microenvironment and the ROS status of surrounding immune cells because increased intracellular ROS in the T cells from tumor-bearing hosts has been described [14]. Cytokines that are abundant in the tumor microenvironment such as tumor necrosis factor (TNF), interleukin (IL)-1β, interferon (IFN)-γ, transforming growth factor (TGF)-β and IL-6 have been shown to

increase both intracellular and extracellular ROS production from epithelial, smooth muscle and pancreatic cells [38, 165, 194]. Thus, strategies to treat cancer via oxidative or antioxidative drugs should take into account the wide panoply of both positive and negative effects of ROS on immunity and cancer progression.

Multiple studies have found a significant role for ROS to control leukocyte recruitment by serving as direct chemoattractants. ROS can directly recruit immune cells in inflamed zebrafish tissue [122] or induce proteins such as thioredoxin that are chemotactic for monocytes, neutrophils and T cells [13]. However, neither of these works used cancer immune surveillance models. Our group has recently linked oxidative stress pathways directly to leukocyte recruitment in cancer [141]. In a study using transplantable melanoma and sarcoma mouse models, we found that activating the antioxidant transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2) induced the cytokine IL-17D, which mediated the recruitment of cancer-eliminating natural killer (NK) cells. Indeed, treatment of cancer cells with Nrf2 agonists led to secretion of IL-17D, NK cell recruitment, and cancer elimination. To our knowledge, this is the first study showing that intrinsic oxidative stress of the tumor cell itself activates mechanisms that lead to immune cell recruitment and immune cell-mediated cancer elimination [141]. Thus, it is possible that cancer cells initiate mechanisms (such as transcriptional activation of antioxidant genes) to overcome oxidative stress, but that the same mechanisms lead eventually to their elimination by the immune system. It is interesting to speculate that the Nrf2/IL-17D pathway may have evolved as the immune system's refutation to the cancer's increased defense mechanisms against oxidative stress. Moreover, ROS might not only influence immune cell infiltration, but also retention and survival at the site of inflammation or cancer, since ROS derived from myeloperoxidase activity can promote paracrine neutrophil survival [86, 156].

ROS can also directly limit tumor progression by augmenting the function of phagocytes and antigen-presenting cells (APCs), often leading to increased anti-tumor T-cell activation. The killing capacity of activated macrophages towards tumor cells, for example, largely depends on ROS production from macrophages [116, 119], that could be further induced if tumor cells were coated with eosinophil peroxidase generating H_2O_2 [118]. H_2O_2 can increase major histocompatibility complex (MHC) class II and co-stimulatory molecules on human dendritic cells (DCs), thereby enhancing T-cell proliferation and activation [140]. Moreover, DCs generate ROS during antigen presentation to T cells [106], and antigen presentation is also influenced by ROS, thus indirectly affecting T-cell stimulation [110]. More evidence that APC-mediated T-cell activation is influenced by ROS activity came from studies showing that macrophages can modulate their secretion of the antioxidant glutathione, which facilitates T-cell activation [5, 55, 120, 154]. On the other hand, the production of glutathione by tumor cells has been suggested as a cancer defense mechanism against macrophage-mediated killing [117].

ROS can also directly activate lymphocytes, including T, B, and NK cells. Oxidation of human ovarian epithelial cancer cells, for example, was shown to enhance T-cell activation from patients in an MHC class I- and II-restricted manner [26]. In line with that, antioxidants directly inhibit T-cell activation, proliferation and IL-2 receptor expression [24, 25, 123]. Moreover, the oxidative status of antigens can modify T-cell receptor (TCR) binding to the antigenic peptide [182], and TCR ligation induces ROS production from T cells [42]. Oxidative stress has also been suggested to promote T-cell polarization into a Th2 phenotype [85]. In B cells, ROS are important for B cell receptor (BCR) signaling [158].

In other instances, ROS can be immune suppressive by their ability to influence or be released from immune suppressive regulatory T cells (T_{Reg}) and myeloid-derived suppressor cells (MDSCs). T_{Regs} can be induced by ROS [90] and are more resistant to ROS than effector T cells [112], which might be a mechanism of cancer immune evasion by favoring an immune suppressive tumor microenvironment. Although most studies found ROS to induce T_{Regs}, one showed that ROS from MDSCs inhibited the maturation of T_{Regs} using murine breast and lung carcinoma cancer models [20]. Some of T_{Reg} cell suppressive functions towards other T cells are mediated by their secretion of ROS [51] or indirectly by their ability to suppress glutathione release from DCs [193]. H_2O_2 has been found to directly inhibit nuclear factor κB (NF-κB)-induced cytokine expression from activated T cells [95, 104]. ROS can also regulate T-cell apoptosis and thereby contribute to T-cell balance under homeostatic and disease conditions [172].

MDSCs are another major suppressive cell type producing and reacting to ROS in the tumor microenvironment. Several tumor-derived cytokines trigger ROS production from MDSCs, which might account for some of MDSC's immunosuppressive functions [59] and maintain them in an undifferentiated state [94]. In a mouse lymphoma model, MDSCs were able to suppress T-cell proliferation and IFNγ production by disrupting the TCR/CD8 complex, which was mediated by overproduction of ROS [113]. MDSCs also suppress T cells by depletion of cysteine and arginine (which are crucial for T-cell activation and proliferation), production of peroxynitrite (which are cytotoxic to T cells), and upregulation of the ROS-generating enzyme cyclooxygenase (COX)-2 in T cells [17, 59, 84, 164]. Additionally, in advanced cancer patients, H_2O_2 derived from granulocytes is suggested to suppress cytokine release from T cells [144].

Early studies suggest that ROS production from NK cells is a necessary event for NK cell cytotoxicity against cancer [49, 50, 136, 167]. On the other hand, monocyte-derived ROS downregulate the expression of activating receptors NKG2D and NKp46 on a certain subtype of NK cells with high cytotoxic ability [138]. Moreover, H_2O_2 in the cancer microenvironment decreases the recruitment of this NK cell subtype [80], suggesting that ROS production is a mechanism of cancer cells to evade NK cell-mediated immunity. Monocyte-derived ROS can also inhibit activation, proliferation and IFNγ secretion as well as induce apoptosis of NK cells [69, 72, 150]. ROS might also play a role in the dysfunction and depletion of NK cells in myelogenous leukemia patients [108]. H_2O_2 from macrophages isolated from melanoma-bearing patients was shown to downregulate CD3 zeta on T cells and NK cells as well as their cytotoxic activity [88]. The documented inhibitory activity of ROS on NK cells implies that the role of Nrf2, a known master regulator of antioxidant responses and an inducer of IL-17D and NK cell recruitment [141], could be to remove ROS in order to promote anti-tumor activities of NK cells.

Proteotoxic stress

Proteotoxic stress [also referred to as "endoplasmic reticulum (ER) stress"] is characterized by the accumulation of misfolded and/or unfolded proteins within the ER of a cell [179]. ER stress occurs when the amount of proteins entering the ER (input) exceeds the ER's processing capacity (output), leading to dysregulation of post-translational modifications that occur within the ER [16]. Because post-translational modifications help proteins form tertiary and quaternary structures, the lack of appropriate modification results in misfolded proteins that accumulate within the secretory pathway, leading to proteotoxic stress [147].

As it relates to cancer, proteotoxic stress can arise from a number of different sources. In fact, many of the "hallmarks of cancer" directly induce proteotoxic stress. For example, aneuploidy induced by mitotic stress can directly contribute to proteotoxic stress through the presence of excess copies of wild type (WT) proteins, which accumulate within the ER and disrupt the organelle's folding capacity [48]. Furthermore, the presence of abnormal proteins that do not fold properly or cannot be modified can also cause proteins to build up within the ER and trigger proteotoxic stress. Abnormal proteins can arise either directly from genetic mutations or indirectly from ROS (oxidative stress) that damage WT proteins (Fig. 2). Clearly there are many different stressors present in cancer cells that have the capability to over-burden the secretory pathway and directly lead to proteotoxic stress.

The accumulation of misfolded proteins and proteotoxic stress leads to the activation of the unfolded protein response (UPR). Although the UPR signaling network does not directly activate immune responses, when the UPR fails to restore ER homeostasis, a form of apoptotic cell death occurs that is characterized by the release of immune-stimulating molecules [176]. This phenomenon is referred to as immunogenic cell death (ICD), distinct from classical apoptosis, which is considered tolerogenic. ICD, on the other hand, is a powerful stimulator of immune cells by causing the release of danger-associated molecular patterns (DAMPs) into the extracellular environment. Examples of DAMPs include proteins such as calreticulin (CRT) and high-mobility group box 1 (HMGB1), and small molecules, like ATP [175]. DAMPs can directly or indirectly stimulate many different types of immune cells, including macrophages, DCs, and T cells [176]. The specific mechanisms by which each immune cell subset is affected by and responds to DAMPs will be discussed throughout this section. ICD is induced when the UPR fails to restore ER homeostasis, often due to the use of chemotherapeutics, such as anthracyclines, oxaliplatin, bortezomib, radiotherapy, and photodynamic therapy [92]. Thus, at the "basal" state, cancer cells can exhibit proteotoxic stress, but when cancer cells are exposed to a higher level of proteotoxic stress, they can undergo cell death and potently activate the immune system through release of DAMPs.

Perhaps the best-explored DAMP is CRT, a normally intracellular transmembrane protein that is translocated to the cell surface (ecto-CRT) during proteotoxic stress. For example, when anthracycline treatment is used to model proteotoxic stress, ecto-CRT is exposed at the cell surface and leads to phagocytosis of the dying cells by immune cells, leading to their activation [124]. In this model system ecto-CRT is both sufficient and necessary to promote immune surveillance of anthracycline-induced proteotoxic stress in colon cancer. These results were corroborated and shown to require the UPR system [128]. Ecto-CRT signals through low density lipoprotein receptor-related protein 1 (LRP1, also known as CD91), a pattern recognition receptor (PRR) that is shared with heat shock proteins. CD91 is expressed on immune phagocytes, and CRT-CD91 signaling promotes phagocytosis and induces the secretion of pro-inflammatory cytokines that ultimately aid in the presentation of tumor antigen [11]. Therefore, this signaling pathway is important for eliciting robust T-cell responses that are critical for tumor elimination.

HMGB1, a nuclear protein involved in chromatin organization, is a DAMP that is released passively into the extracellular environment during ICD. HMGB1 can signal through toll-like receptor 4 (TLR4) expressed on DCs, resulting in MyD88-mediated pro-inflammatory cytokine production [6]. In addition, the receptor for

advanced glycation end-products (RAGE), expressed by macrophages, can also recognize HMGB1 and induce the production and secretion of pro-inflammatory cytokines [87]. Each of these signaling events is important for eliciting anti-tumor immune responses and therefore plays important roles in the immune surveillance of cancer cells in a manner dependent on antigen-presenting cells. On the other hand, HMGB1-RAGE signaling can also induce inflammatory responses that promote tumor progression and are associated with worse prognosis in certain patients [121, 157]. Because it is released by dying cells rather than induced by the UPR, HMGB1 presumably could activate the immune system when released by stressors other than proteotoxic stress.

ATP is another DAMP that is released into the extracellular environment in the event of ICD. During proteotoxic stress, ATP is actively secreted from cells, where it can either induce local inflammation or act as an "eat me" signal. Secreted ATP can be recognized by the purinergic receptor P2X7 that is expressed on DCs. This signal induces inflammasome activation and drives the secretion of IL-1β, a highly pro-inflammatory cytokine [64]. Furthermore, secreted ATP can also act as a "find me" signal by recruiting phagocytic cells [53]. In either case, it is clear that secreted ATP acts to promote immune recognition and clearance of cells undergoing proteotoxic stress.

In addition to DAMPs, proteotoxic stress can stimulate general inflammation through the activation of NF-κB and Jun N-terminal kinase (JNK). NF-kB is a master regulator of inflammation, and upon activation, induces the production of a number of pro-inflammatory genes. Proteotoxic stress has been shown to activate NF-kB in several model systems. In HeLa cells, 2-deoxyglucose can induce ROS and misfolded proteins, leading to proteotoxic stress and NF-κB activation [126]. In primary fibroblasts, thapsigargin-induced ER stress can promote NF-κB activation by attenuating translation. This increases the ratio of NF-κB to IκB (owing to the short half-life of IκB), thereby freeing NF-κB to translocate into the nucleus when the UPR is activated [40]. Proteotoxic stress also activates JNK directly via interaction between JNK and components of the UPR [173].

Although the action of tumor-derived proteotoxic stress on immune cells is generally considered anti-tumorigenic, in certain contexts it has also been shown to promote tumor growth. For example, activation of NF-κB is well known to promote cancer progression [82] and in some circumstances, HMGB1-RAGE signaling can provide "wound healing" signals to also facilitate cancer growth. In addition, several groups have demonstrated a pro-tumorigenic role for proteotoxic stress by showing that it acts in a cell extrinsic manner on myeloid cells to facilitate tumor growth [35, 198]. Evidence for this phenomenon is that macrophages cultured in the conditioned medium of ER-stressed breast, lung, or melanoma cancer cells become activated and begin secreting pro-inflammatory/tumorigenic cytokines and enzymes that suppress T-cell tumoricidal activity [103]. Furthermore, DCs cultured in the presence of conditioned media of ER-stressed cancer cells downregulate cross-presentation of high-affinity antigens and fail to effectively cross-prime $CD8^+$ T cells, leading to diminished $CD8^+$ T-cell infiltration in vivo [102]. Finally, it has also been demonstrated that transmissible ER stress is pro-angiogenic, as macrophages cultured in the presence of conditioned media of ER-stressed breast cancer cells express the angiogenic factor vascular endothelial growth factor (VEGF) in vitro [36]. Together, these results show that ER stress within the tumor microenvironment has the capacity to reshape myeloid cells to promote tumor growth.

Mitotic stress

Mitotic stress is characterized by the duplication or deletion of whole or partial chromosomes from the genome of a cell, which can occur through a variety of means. Most commonly, mitotic stress is mediated via chromosome instability (CIN). CIN refers to the ability of cells to rapidly lose or gain chromosomes during cell division [89]. This occurs due to mis-segregation of individual chromosomes during cellular replication, wherein DNA is distributed unequally to daughter cells [48]. As a result, cells are generated that possess an abnormal, or "non-diploid" number of chromosomes, a state referred to as "aneuploidy". Other mechanisms that induce aneuploidy include failure in cytokinesis (endoreplication), where DNA is duplicated but the cell does not undergo cytokinesis, and cell–cell fusion, where two cells physically connect their plasma membranes and cytosol and combine DNA. Both of these mechanisms give rise to daughter cells that contain twice the amount of DNA than parental cells and feature mitotic stress [89].

Aneuploidy and CIN are closely related, each being an extremely common feature in cancer. It has been estimated that greater than 70% of all cancers display aneuploidy [111], although whether this is a cause or consequence of the disease is highly debated. CIN can occur through three major mechanisms: mitotic checkpoint defects (resulting in premature chromosome segregation), centrosome overduplication (resulting in improper attachments between microtubules and the kinetochore and frequent chromosome mis-segregation), and faulty sister chromatid cohesion (causing premature separation of sister chromatids) [48]. Many genes involved in these processes are direct transcriptional targets of E2F and/or p53 [89]. Aberrations in these pathways caused by either mutations or overexpression/gene duplication have the potential to induce mitotic

stress and CIN that culminates in aneuploidy, which can be sensed by immune cells in a variety of different ways.

A direct consequence of mitotic stress induced by CIN and aneuploidy is that it causes imbalances in the composition of cellular proteins, which affects the folding capacity of the ER and leads to proteotoxic stress (Fig. 2). In this sense, all of the surveillance mechanisms relevant in proteotoxic stress also occur during mitotic stress (see "Proteotoxic stress"). Specifically, hyperploidy is known to be immunogenic by inducing surface expression of the DAMP calreticulin (ecto-CRT) [22]. Tetraploid colon, lung, and fibrosarcoma cancer cells readily proliferate and maintain their increased DNA content and ecto-CRT expression in immunodeficient, but not in immunocompetent, mice. In immune competent mice, growth of tetraploid cancer cells is delayed, and tumors that do grow exhibit reduced DNA content and ecto-CRT exposure relative to tumors grown from immune-deficient mice [151]. These results suggest an active immunoediting mechanism operates against mitotically stressed cells. Furthermore, colon cancer cells are susceptible to drug-induced tetraploidization only in the absence of the tumor suppressor Tp53, and tetraploid $Tp53^{-/-}$ colon cancer cells are only able to form tumors in immune deficient, but not immune competent, mice [15]. This result suggests that the mitotic stress induced by tetraploidy is particularly oncogenic in the context of deficient immune surveillance, and that tetraploidy (and associated mitotic stress) is immunogenic. Finally, it has also been shown that hyperploid cancer cells stimulate NK cell-mediated anti-cancer immunity. Specifically, hyperploid human erythroleukemic, colon and liver cancer cells can activate the cytotoxic activity of NK cells via the expression of ligands for NK activating receptors such as NKG2D and DNAX accessory molecule (DNAM-1) [1]. Together, these findings strongly suggest that mitotic stress associated with hyperploidy (specifically tetraploidization) is immunogenic and induces anti-tumor immune surveillance by NK cells, and that this phenomenon is broadly conserved across multiple cancer types.

Mitotic stress can also promote cancer progression through the induction of inflammatory cytokines that support tumor growth [135]. In a mouse model of colon tumorigenesis whereby mice are haplosufficient for Shugoshin-1 ($Sgo1^{+/-}$), a gene involved in the maintenance of chromosome cohesion during cellular replication, CIN and DNA damage results, leading to the secretion of pro-inflammatory cytokines that promote tumorigenesis. Specifically, $Sgo1^{+/-}$ mice display increased expression of the pro-inflammatory factors COX-2 and IL-6, each of which has been shown to have a role in promoting colon cancer formation. This cytokine response is dependent on DNA damage response proteins, supporting the role of mitotic stress in mediating this response [191]. Indeed, even in human cancers, a similar finding has been reported, whereby CIN-induced DNA damage signaling leads to the secretion of pro-tumor inflammatory cytokines [137]. In a slightly different mouse model of CIN-induced tumorigenesis whereby the gene flap endonuclease 1 (*Fen1*) is mutated to induce genomic instability, CIN is associated with tumor progression through predisposition to chronic inflammation mediated by NF-kB. Specifically, mice harboring the mutant *Fen1* showed significantly higher levels of inflammatory NF-kB target genes compared to WT mice [201].

Mitotic stress can also trigger immune surveillance through the induction of cellular senescence, which has been shown to be immunogenic in certain circumstances. Senescence is a permanent state of cellular growth arrest that can be triggered by various stressors. In cancer, senescence acts as a tumor suppressive mechanism by inhibiting cellular proliferation and tumor growth, but can also favor tumor growth in certain instances by promoting inflammation [32]. Mitotic stress occurring in cancer cells can induce senescence by activating pathways that promote both cell cycle arrest and survival [174]. Introducing an oncogenic activating H-Ras mutation (H-RasV12) into human fibroblasts resulted in enhanced survival of cells with mitotic spindle and chromatin defects. These cells also featured induction of the key senescence effectors p21 and p16, further supporting that mitotic disruption and enhanced survival are linked during senescence [46]. As it relates to immune surveillance, senescence is immunogenic by causing the secretion of inflammatory cytokines, which can both promote and inhibit tumor progression. This is referred to as the senescence-associated secretory phenotype (SASP) [29]. The SASP is mediated primarily by the transcription factors NF-kB and CCAAT/enhancer binding protein beta (C/EBPβ) and consists of a broad range of secreted factors, including chemokines/cytokines, growth factors, and matrix-remodeling enzymes, among many others (reviewed in [96]). Together, these secreted factors produce a rich pro-inflammatory microenvironment that recruits immune cells that can either promote or inhibit tumor growth, depending on the circumstance. For example, in an oncogene-induced model of senescence in murine hepatocytes, senescent cells are subject to $CD4^+$ T-cell-mediated immune clearance that is also dependent on monocytes/macrophages, and in the absence of immune surveillance, pre-malignant hepatocytes develop into hepatocellular carcinomas [81]. NK cells also mediate immune surveillance of senescent cells. NKG2D-dependent elimination of hepatocellular carcinomas can be mediated by p53-dependent chemokine production by senescent tumor cells [76]. Alternatively, the SASP has also been demonstrated to promote tumor progression. Using a model of DNA damage-induced senescence on pre-malignant epithelial cells, the SASP induced epithelial-to-mesenchymal transition and invasiveness, two hallmarks

of malignancy. These phenotypic changes were dependent on the inflammatory cytokines IL-6 and IL-8 [30]. These examples clearly demonstrate how senescence induces immune surveillance that ultimately can either promote or inhibit tumor progression, depending on the context.

Mitotic stress and CIN are also known to induce immune surveillance in invertebrates [152]. Indeed, inducing CIN in proliferating *Drosophila* larval tissue resulted in the activation of innate cellular signaling in cells with CIN. Included in this innate signaling was the activation of matrix metalloproteinase 1, which is responsible for recruiting hemocytes (innate insect immune cells) to the site of CIN and providing the necessary signals for effective elimination of CIN cells [99]. This pathway appears to be mediated by JNK, as knockdown of JNK signaling resulted in death of CIN cells [187]. These studies demonstrate a cell-intrinsic role for mitotic stress and CIN in inducing innate immunity in insects, suggesting a conserved mechanism for eukaryotic organisms for responding to mitotically stressed cells.

DNA damage

DNA damage is a change in DNA structure that can occur in cancer cells intrinsically during the "stress" of extensive replication or as a direct result of mitotic and/or oxidative stress (Fig. 2). In addition, it can be caused by extrinsic stresses such as viral infection, radiation, UV light or chemotherapy [98]. Apart from causing mutations that can lead to the formation of neoantigens activating the immune system, DNA damage can also result in the accumulation of ectopic DNA particles that can function as DAMPs [83] as well as in the upregulation of stress ligands activating immune receptors [62]. This section will focus on the DNA damage-induced expression of stress ligands as well as on immune surveillance activities induced by DNA damage-associated DAMPs rather than the well-described formation of neoantigens that has been reviewed elsewhere [98].

DNA damage can directly alert the immune system by inducing MHC class I-like ligands of activating receptors present on immune cells [21]. NK cells, γδ T cells, αβ $CD8^+$ T cells and NKT cells express the receptor NKG2D that can bind to stress ligands [100], which become upregulated after stress signals, especially in cancer cells [161]. DNA-damaging conditions such as ionizing radiation (IR), damaging agents or synthesis inhibitors can induce the expression of several of these ligands, and this depends on the DNA damage response (DDR) machinery [62, 63]. Similarly, ligands of the activating receptor DNAM-1 expressed by NK and T cells were found to be upregulated by chemotherapeutic treatment of multiple myeloma cells, and this was counteracted by inhibiting members of the DDR machinery [162, 163]. Recently, it has been suggested that fibroblasts can acquire APC-like functions by their ability to activate naïve $CD8^+$ T cells in response to DNA damage. Treatment of fibroblasts with a DNA-damaging agent induced their expression of MHC class I molecules as well as multiple NKG2D and DNAM-1 ligands [169]. In addition to DNA damage alerting the immune system via stress ligands, the damaged DNA itself can be sensed by the DDR, leading to a senescent state in which inflammatory cytokines are secreted [137]. Indeed, agents that promote double stranded (ds) DNA breaks have been shown to induce inflammatory genes [18]. Moreover, inhibiting the DDR machinery impairs cytokine induction [127] and NK and T-cell dependent tumor regression [168].

If enough damage occurs, DNA can undergo fragmentation and leak into the cytosol or extracellular milieu. In this scenario, DNA itself is a DAMP that is sensed by PRRs resulting in the downstream production of cytokines such as type I IFNs that normally act to initiate anti-viral responses [77]. In typical anti-viral immune responses, PRRs recognize viral nucleic acids, leading to the production of type I IFNs and activation of T-cell responses. It is now believed that the same responses can also be initiated from sensing of endogenous DNA particles that are found in ectopic locations (extranuclear or extracellular), which can occur during cancer as a result of DNA damage. Cytosolic DNA resulting from extensive replication or defects in the DDR in the cancer cell itself can bind to cancer cell-expressed receptors that activate immune surveillance pathways. Extracellular DNA resulting from DNA damage-induced apoptosis, necrosis or leakage can be sensed by receptors on immune cells or non-immune cells in the tumor microenvironment, inducing innate and subsequent adaptive immunity. Type I IFNs produced by either malignant cells or DCs in the tumor microenvironment are therefore mediators of the pathways underlying cancer immune surveillance in response to DNA damage, underlined by their requirement for an optimal anti-cancer response after radiation or chemotherapy [160]. In contrast, induction of type I IFNs by DNA damage might also favor tumor growth because of IFN's known ability to upregulate tumor programmed cell death ligand 1 (PD-L1), an immune suppressive molecule [12, 196].

Since DNA is sensed by PRRs, the role of DNA damage in controlling immune responses in cancer has been studied by examining the role of specific PRRs or their signaling pathways in cancer progression. We review below the following PRRs/signaling pathways: endosomal receptors—TLR3, TLR7, TLR8, and TLR9; cytosolic receptors—cyclic GMP–AMP synthase (cGAS)/stimulator of IFN genes (STING), absent in melanoma (AIM) 2, and retinoic acid-inducible gene (RIG) I-like receptors (RLRs).

TLR3 binds to endosomal dsRNA and serves to alert the immune system to viral infection, but can also promote

cancer clearance. For example, signaling through TLR3 in DCs and other APCs can activate anti-tumor NK cells, presumably due to dsRNA released by cancer cells [3, 107]. *Tlr3*$^{-/-}$ mice featured an increased tumor burden in a mouse model of prostate cancer, which could be counteracted by administration of the TLR3 ligand polyinosinic-polycytidylic acid [poly(I:C)], leading to immune surveillance by T and NK cells [27]. Poly(I:C) administration has also been shown to reduce lung cancer growth, mediated by Th1 and Th17 immunity [57] and is currently investigated in clinical trials as a cancer vaccine adjuvant [114]. Chemotherapeutic agents can induce the production of type I IFNs in response to TLR3 signaling, resulting in chemokine release [160]. Moreover, treatment of prostate cancer cell lines in vitro with TLR3 agonists induces inflammatory molecules that had the potential to recruit immune cells, suggesting that a TLR3-mediated anti-cancer immune response could be directly initiated by signaling inside the cancer cell itself [60].

The closely related TLRs 7 and 8, which recognize single-stranded (ss) RNA, are popular targets for cancer immune therapy. Their agonists induce cytokine and chemokine secretion, macrophage activation and cellular immunity through pathways downstream of the transcription factor NF-κB [146]. Although exogenously used in cancer immune therapy, TLR7/8-mediated immune surveillance has not been documented. However, TLR7 has been suggested to promote chemoresistance when expressed by cancer cells instead of antigen-presenting cells, even in *Tlr7*$^{-/-}$ mice [23].

TLR9 binds to endosomal CpG DNA or oligodeoxynucleotides and its expression has been detected in a number of cancer cell lines and human cancer biopsies. High expression of TLR9 in cancer has been associated with both poor (glioma, prostate cancer, esophageal adenocarcinoma) and good (triple-negative breast cancer, renal cell carcinoma) prognosis [142]. The mechanisms of TLR9's opposing roles in cancer cells have not been fully elucidated, and it is unclear if they are completely immune-related. However, TLR9 agonists are currently investigated for use in cancer immune therapy because of their ability to directly induce activation and maturation of plasmacytoid (p)DCs and subsequent downstream adaptive immunity, and to enhance differentiation of B cells into plasma cells [91]. On the other hand, one recent study found that TLR9 signaling in tumor-infiltrating myeloid cells promoted tumor re-growth after radiation by inducing tumor-promoting inflammation and re-vascularization [61].

The cGAS/STING pathway detects cytosolic DNA accumulated in response to DNA damage [78, 79]. One hypothesis for STING-mediated anti-cancer immunity is that DNA from necrotic tumor cells is engulfed by DCs and triggers STING signaling inside the DCs. Accordingly, STING-deficient mice feature defective T-cell responses in melanoma [188] and glioma [125], and STING is required for type I IFN-mediated anti-tumor effects after radiation [41]. Additionally, loss of STING has been suggested as an escape mechanism of damaged or pre-malignant cells to evade immune surveillance [2, 190, 202]. Moreover, STING agonists are proposed to have potential as a cancer immune therapy agent through their activation of DCs and production of IFNs [97].

Absent in melanoma (AIM) 2 is an intracellular dsDNA sensor that is part of a unique multiprotein complex called the inflammasome, which mediates the secretion of IL-1β and IL-18. Since these two cytokines strongly promote inflammatory responses, AIM2 has been studied in the context of inflammatory cancers, especially those in the gut, where it was shown that *Aim2*$^{-/-}$ mice develop more colitis-associated cancer [105, 186]. As its name implies, AIM2 is downregulated in a variety of cancers and cancer cell lines [43, 45, 132], presumably because it prevents cancer progression, and cancer cells must lose expression of AIM2 to survive anti-tumor responses. Indeed, a recent study proposes that its expression renders mice less resistant to DNA ds-breaks caused by IR and chemotherapeutic agents, which could point towards an inflammasome-mediated role in cancer cell susceptibility to IR and chemotherapy [73].

RLRs recognize cytoplasmic RNA, increasingly present after IR. They include RIG-I, melanoma differentiation-associated protein (MDA)-5 and laboratory of genetics and physiology 2 (LGP2), which is a negative regulator of the former two [185]. Their signaling pathways converge on the recruitment of NF-κB and IRF3, subsequently activating type I IFN production. It has been demonstrated that RIG-I became activated by binding to tumor-endogenous RNA translocating to the cytoplasm after IR and chemotherapy, which resulted in IFN production that was blocked by LGP2 [134, 185]. Ectopic expression of MDA-5 in prostate cancer cells led to eradication of established tumors by activating innate and adaptive immunity via IFN [197]. These studies support the use of RLR agonists for cancer immune therapy [52, 107, 130, 145] although some of the effects are attributed to indirect immune activation by cancer cell apoptosis rather than direct activation of the immune system [47, 93].

Metabolic stress

Cancer cells feature a number of alterations in their metabolism and on the other hand can also influence the metabolic status of their environment. Due to their rapid and extensive replication, cancer cells are in high need for metabolic nutrients and oxygen, creating an altered microenvironment

of hypoxia, low pH and/or nutrient deprivation. Metabolic stress can be defined as any sort of cellular stress caused by increased need for ATP, elevated biosynthesis of macromolecules or altered redox balance [19]. Thus, it is closely correlated with the before-mentioned forms of stress such as oxidative, proteotoxic, mitotic or DNA damage stress (Fig. 2). One well-characterized metabolic effect occurring in cancer is the Warburg effect, which refers to a shift from oxidative phosphorylation to oxygen-independent glycolysis, a faster but less efficient way to generate ATP under hypoxic conditions [180]. As a result, a tumor cell is in abnormally high demand for glucose uptake from the surrounding tissue. This section will focus on the control of immunity by several key processes resulting from metabolic stress, including hypoxic pathways, autophagy, mitochondrial stress, and oncometabolites.

As mentioned above, changes in metabolism can cause and be caused by hypoxia in the tumor microenvironment of solid cancers, which can influence infiltrated immune cells in different, mainly suppressive, ways. Hypoxia can directly inhibit the cytotoxic activity of NK cells [143], or lead to downregulation of stress ligands on the tumor cell surface [155]. It also decreases T-cell survival [166], IL-2 secretion [203] and increases the expression of the inhibitory ligand PD-L1 on tumor cells [10]. Under hypoxic conditions, tumor cells release a number of immune suppressive cytokines such as TGF-β, which inhibits T-cell proliferation and activation, promotes suppressive T_{Reg} development, inhibits antigen presentation by DCs and decreases the expression of activating NK cell receptors [189]. Together with IL-10 also released in response to hypoxia, TGF-β induces the differentiation of macrophages into a tumor-promoting M2 phenotype [70]. VEGF induced by hypoxia suppresses DC maturation and antigen presentation [58], increases their expression of PD-L1 [37] and promotes the accumulation of MDSCs in tumor tissue [58]. Moreover, it was shown in an ovarian cancer model that tumor cells can secrete the T_{Reg}-recruiting chemokine CCL28 under hypoxic conditions [54]. COX-2 expression is upregulated in cancer cells in response to hypoxia [66], resulting in effector T cell and DC suppression as well as in T_{Reg} and MDSC activation [159, 184, 195]. Hypoxia might not only be immune suppressive. Hypoxia-experiencing tumor cells release higher amounts of ATP, which can serve as a DAMP for inflammasome-induced immune responses [70], as described in the section about "DNA damage".

Another direct result of metabolic stress is autophagy, the process in which a cell degrades, reassembles and recycles its components to survive under nutrient and energy starvation conditions [7]. Because autophagy modulates the cancer cell secretome and surface proteome, it can result in the release of immune-activating DAMPs such as ATP, ecto-CRT, or HMGB1 [177], and other secreted proteins such as cytokines [177] (see "DNA damage" and "Proteotoxic stress"). Autophagy can also promote DC and T-cell recruitment into the tumor bed and initiate immune responses [109]. In immune cells, autophagy can promote proliferation, antigen presentation, cell activation and cytokine secretion [74, 133, 177]. Cancers can also use hypoxia-induced intrinsic autophagy as an immune evasion mechanism because increased autophagy suppresses antitumor immune responses [4]. Additionally, it has recently been shown that cancer cells use autophagy-mediated degradation of granzyme B secreted from NK cells to evade lysis [9].

Metabolic stress can also result in damage of mitochondrial (mt) DNA due to hyperactive mitochondria in response to increased energetic requirements of cancer cells. Compared to nuclear DNA, mtDNA is more susceptible to damage because it is not associated with histones and constantly exposed to high ROS levels [178]. Therefore, immune responses similar to the ones activated in response to nuclear DNA damage (see "DNA damage") can also be initiated by mtDNA damage, including activation of TLR9 [181, 199], the NLRP3 inflammasome [115, 153], and cGAS/STING [183].

Another result of the unique metabolism observed in cancer cells is the production of metabolic byproducts that are different from those of normal cells. These "oncometabolites" include lactate (or lactic acid), succinate, and 2-hydroxyglutarate (2-HG), among others [31]. Oncometabolites accumulate within the tumor microenvironment and have the capability to affect healthy host cells residing there. As described below, oncometabolites have been shown to regulate immune-mediated surveillance of cancer cells by directly affecting a broad range of immune cells, including macrophages, monocytes, NK cells, MDSCs, $CD8^+$ T cells, and DCs.

One prominent effect of the altered metabolic state of cancer cells is the production and accumulation of lactate. This depends on lactate dehydrogenase (LDH), the enzyme responsible for catalyzing the formation of lactate from pyruvate in the final step of the glycolytic pathway [8]. LDH is frequently upregulated in various cancers and acts as an important control point for metabolic regulation in cancer cells. Lactate has been shown to promote tumor growth by negatively affecting immune surveillance in a number of different contexts. For example, tumor-associated macrophages can be functionally polarized toward a pro-tumor M2 phenotype by lactate derived from murine lung cancer cells [28]. This phenotypic change is mediated through HIF1α and appears to be critical for tumor growth, as lung tumors grown in mice lacking pro-tumor M2 macrophages grew significantly slower than tumors in WT mice [28]. This is in line with similar reports showing that during wound healing, extracellular lactate stimulates the

production of the immunosuppressive M2 factors VEGF and TGF-β from macrophages [171]. Lactate also suppresses production of the pro-inflammatory cytokine TNF. Co-culturing monocytes with melanoma cells reduced the ability of monocytes to produce TNF, but this effect was not observed if the melanoma cells were pre-treated with oxamic acid, an LDH inhibitor that prevents the production of lactate [44].

NK cells are also negatively affected by tumor-derived lactate, both directly and indirectly via MDSCs [75]. In murine pancreatic cancer cells, knockdown of *LdhA* (and subsequent lack of lactate production) delays tumor growth relative to WT tumors, and NK cells from knockdown tumors have improved cytolytic function compared to NK cells from WT tumors. Matching this result, in vitro treatment of NK cells with lactate inhibits cytolytic function and decreases expression of cytolytic granules and the activating receptor NKp46. Furthermore, lactate appears to stimulate the development of MDSCs, a cell type capable of directly inhibiting NK cytotoxicity. MDSCs are present in higher abundance in mice bearing WT pancreatic tumors compared to mice bearing tumors that cannot produce lactate, and in vitro lactate treatment increases the generation of MDSCs [75]. These data show how tumor growth can be promoted by lactate through the functional impairment of NK cells and induction of MDSCs.

Tumor-derived lactate can also inhibit the function of $CD8^+$ T cells. Co-culturing human $CD8^+$ T cells with lactate-producing melanoma cells reduces T-cell proliferation and production of pro-inflammatory cytokines, but this effect is not observed using melanoma cells that have been pre-treated with oxamic acid and cannot produce lactate. Similarly, in human cancer patients, serum lactate levels and tumor burden are positively correlated, suggesting that lactate provides a positive signal for tumor growth [56]. Together, these results support that tumor-derived lactate induces inhibitory effects on adaptive immune cells and acts to suppress immune surveillance and promote tumor growth.

LDH, the enzyme responsible for producing lactate in tumor cells, has also been implicated in regulating immune–cancer interactions [8]. Indeed, glioma-derived LDH isoform 5 induces the expression of NKG2D ligands on myeloid cells, which subsequently decreases the expression of NKG2D on NK cells themselves. As a result of these interactions, NK cell-mediated killing of glioma cells is decreased [34]. Clearly tumor-derived lactate can have broad-reaching effects on many different types of immune cells and generally acts to inhibit immune-mediated cancer surveillance.

The oncometabolite 2-HG can promote tumor growth by acting cell-intrinsically to induce epigenetic reprogramming in cancer cells that can affect their ability to be recognized by immune cells. In gliomas, these epigenetic changes influence genes that regulate immune surveillance. The majority (~80%) of gliomas feature gain-of-function mutations in the enzyme IDH1 or 2, which causes the enzymes to produce the oncometabolite 2-HG instead of NADPH [192]. In gliomas harboring this activating mutation, NKG2D ligands are down regulated via epigenetic silencing, and these cancers thereby acquire resistance to NK cells in a manner dependent on 2-HG [200].

Not all oncometabolites are immune suppressive like lactate and 2-HG. Succinate, an intermediate in the citric acid cycle, has been shown to stimulate immune cells and could potentially induce immune surveillance. The accumulation of succinate occurs in rare cancers with mutations in genes coding for succinate dehydrogenase, such as paragangliomas and pheochromocytomas [39, 65]. In these cancers, levels of succinate are elevated, and so are HIF-1α and HIF-1α-related genes, suggesting that hypoxic pathways are also activated in these cancers [131]. Succinate is a known inflammatory signal that induces IL-1β secretion from macrophages in the context of LPS-induced activation [170]. Succinate can also act cell-extrinsically by signaling through its receptor GPR91 [71], leading to production of pro-inflammatory cytokines in DCs [139]. While it has not yet been empirically tested if these effects promote or inhibit cancer progression, one could speculate that the immune stimulatory effects of succinate would act to enhance immune surveillance and inhibit tumor growth. In this sense, succinate appears to oppose the immune inhibitory, tumor-promoting effects of lactate and 2-HG.

Concluding remarks

Immune cells make up a surprisingly large component of a tumor mass, and the activity of these cells plays an important role in dictating the outcome of cancer (i.e., rejection, equilibrium, progressive growth, metastasis, etc.). Here, we have focused on how the activity of immune cells is regulated by intrinsic stress occurring in cancer cells, and how this regulation subsequently affects tumor progression. We have defined five unique stress pathways that occur in cancer and described how each pathway affects immune surveillance of cancer. These stress pathways are highly interrelated, have broad-reaching effects on many different immune cells, and can both promote *and* inhibit anti-tumor immunity, depending on the context (Figs. 1, 2). Clearly, the regulation of immune cells by tumor cells is complex and can ultimately either inhibit or support tumor progression. In this sense, it becomes increasingly important to fully understand the intricate and sometimes paradoxical relationship between cancer and immune cells, since

these interactions could become the basis for future cancer therapies.

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