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Damage-associated molecular patterns in cancer: A double-edged sword

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Abstract

Damage-associated molecular patterns (DAMPs) are released in response to cell death and stress, and are potent triggers of sterile inflammation. Recent evidence suggests that DAMPs may also have a key role in the development of cancer as well as in the host response to cytotoxic anti-tumor therapy. As such, DAMPs may exert protective functions by alerting the immune system to the presence of dying tumor cells, thereby triggering immunogenic tumor cell death. On the other hand, cell death and release of DAMPs may also trigger chronic inflammation and thereby promote the development or progression of tumors. Here, we will review the contribution of candidate DAMPs and their receptors and discuss the evidence for DAMPs as tumor-promoting and anti-tumor effectors as well as unsolved questions such as DAMP release from non-tumor cells as well as the existence of tumor-specific DAMPs.

Keywords

Cell death; HMGB1; ATP; FPR1; Calreticulin; chemotherapy; radiation

Introduction

Cancers have been described as “wounds that do not heal”[1], suggesting that multiple components of the wound healing process also contribute to carcinogenesis. This notion is supported by a landmark study by Bissel and colleagues, demonstrating that wounding strongly promotes the development of tumors following injection of Rous Sarcoma virus[2]. Likewise, clinical evidence suggest more common recurrence of tumors in resection margins, i.e. sites in which wound healing occurs, often with poorer differentiation and dismal prognosis[3]. Together, these studies suggest that injury and subsequent wound healing

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promote the development of cancer. Injured or stressed cells release a plethora of mediators, termed damage-associated molecular patterns (DAMPs), that potently trigger sterile inflammation. DAMPs represent a large range of chemically unrelated mediators entities such as High Mobility Group Box 1 (HMGB1), S100 proteins, hyaluronan, heat shock proteins, ATP and calreticulin that are retained inside the cell in the healthy state and only released following stress or cell death, thus allowing the host to sense and react to damage via specific DAMP receptors. While DAMPs were initially considered to be exclusively released from necrotic cells, recent evidence suggest that specific forms of programmed cell death such as necroptosis and immunogenic cell death (ICD) following anti-cancer therapies[4–7] can also trigger DAMP emission into the extracellular space. DAMP-mediated sterile inflammation is an important component of a wide range of diseases including atherosclerosis, myocardial infarction, autoimmune diseases, and cancer[8]. As there are several excellent reviews on DAMPs and their receptors[4, 8–10], we will selectively focus on their involvement in cancer in this review.

There are multiple parallels between innate immune responses to pathogens and cell death, such as the use of specific pattern recognition receptors (PRRs), and the occurrence of neutrophils and inflammation at sites of infection or injury. Hence, these pathways can be classified as a common danger response system that can be activated by either pathogen-associated molecular patterns (PAMPs) or DAMPs in order to combat danger and restore tissue homeostasis. DAMPs could not only warn the body about the presence of tissue injury in sterile conditions but also in the setting of infection, e.g. when pathogens induce cell death, and thereby trigger more profound immune responses. In analogy, death of premalignant or malignant cells might allow a more potent anti-tumor response or immunosurveillance. As such, there is accumulating evidence that anti-tumor therapies including radiation therapy and select chemotherapeutic agents not only trigger direct cytotoxic effects, but also contribute to subsequent priming of the immune system and immune-mediated anti-tumor responses[7, 11, 12]. On the other hand, inflammation is a double-edged sword that may not only trigger anti-tumor immune responses but also promote carcinogenesis in many settings (Table 1). Failure of DAMPs to elicit an effective anti-tumor response might turn DAMP-induced inflammation into a tumor-promoting mechanism[13, 14] – similar to wound healing, which often becomes maladaptive when injury is chronic[15]. Here, we will discuss the possible roles of DAMPs in cancer, focusing not only on DAMPs as mediators of immunogenic tumor death but also the possible roles of DAMPs as triggers of tumor-promoting inflammation, as well as changes in the tumor microenvironment.

1. Release of DAMPs in tumors or their environments

Although we are only starting to understand the functions of DAMPs in malignancy, it has become evident that DAMPs are released by a wide range of tumors (Table 1). DAMPs are released in response to different modes of cell death (apoptosis, necroptosis, necrosis) and their release is regulated by different mechanisms and at different stages of cell death. Although it is believed that necrotic and necroptotic cell death are more inflammatory than apoptotic cell death, this concept needs to be more rigorously tested in context-specific settings[16]. As tumors grow, metabolic demands increase and cancer cells are inevitably exposed to metabolic, hypoxic, genetic and/or mechanical stress, leading to the induction of

cell death, often visible as a necrotic tumor core[17]. Whether this type of cell death is largely necrotic, necroptotic, apoptotic or a mix of all these remains to be determined and is likely to be tumor-specific. Although there is evidence for DAMP release in the setting of spontaneous tumor cell death, e.g. a strong increase of extracellular ATP and adenosine within tumors[18, 19], the release of DAMPs is much better documented during anti-tumor therapy[20–22]. As such, therapeutic interventions such as chemo- and radiotherapy and oncolytic viruses trigger profound DAMP release[12, 23, 24]. The predominant form of cell death by these therapeutic interventions appears to be apoptosis[11, 12], but other forms of cell death also participate[17, 25, 26], and the mode of cell death likely determines the spectrum and activity of released DAMPs. Finally, cancer cells may also release DAMPs through stress pathways that either precede or are not directly related to cell death. Treatment with anthracyclins or photodynamic therapy result in the early translocation of calreticulin (CRT) to the cell surface before affected cells exhibit biochemical signs of apoptosis[5, 6]. CRT is not a classical DAMP as it is not secreted and appears to be selectively operating as an “eat me” signal to stimulate the engulfment of apoptotic cells by dendritic cells (DC)[5, 27]. Mechanistically, surface exposure of CRT is triggered by endoplasmic reticulum (ER) stress[6]. Another example is the release of ATP, which is mediated by active secretion from dying cancer cells preceding the post-mortem release of HMGB1[28]. ATP release in this setting is triggered by activation of caspases, which contribute to the redistribution of ATP from lysosomes to autolysosomes as well as the opening of pannexin 1 channels[28]. Extracellular ATP can be converted into adenosine, which acts through distinct receptors that often result in immunosuppressive effects opposing the immunostimulatory effects of ATP. There is accumulating evidence on adenosine accumulation in the tumor environment, thus creating an immunosuppressed “tumor-friendly” niche[19]. Increased levels of extracellular adenosine are the result of increased expression of ectonucleotidases CD39 and CD73[29]. In addition, several tumors show altered purine metabolism, which facilitates the production of adenosine or reduces its degradation[19]. Moreover, some DAMPs such as HMGB1 cannot only passively leak from dying cells but also be actively secreted via mechanisms that require posttranslational modifications such as acetylation and translocation from the nucleus to the cytosol[30]. In hypoxic hepatocellular carcinoma, HMGB1 is almost exclusively located in the cytoplasm[31] and hypoxia is sufficient to trigger HMGB1 release in carcinoma cell lines[31], suggesting that cell death-independent HMGB1 secretion is also operative in cancer. Recent publications show lower nuclear HMGB1 staining in a large percentage of human tumor samples, which might – rather than indicating lower HMGB1 expression by the tumor – also indicate increased HMGB1 secretion[32]. Indeed, human malignant mesothelioma biopsies have been shown to display a variable degree of HMGB1 cytoplasmic staining, absent in normal pleura, that correlated with tumor stage[33]. Many members of S100 protein family, which serve as intracellular Ca^{2+} sensors under physiologic conditions but also as DAMPs under pathologic conditions, exhibit cancer-type-specific patterns of dysregulated expression, with most evidence pointing towards overexpression and cancer promotion[22]. S100 proteins lack a leader sequence, precluding secretion via the classical Golgi pathway. Whereas S100A8/A9 can be actively secreted in a microtubule-and proteinase kinase C-dependent manner, both S100A8/A9 and S100B can also be passively released by injured tissues[34]. However, the precise mechanisms, by which they are released in cancer, are currently unknown. Interleukin (IL)-1α is released by many

cell types upon activation or following necrosis and IL-1 signaling has been implicated in the response to necrotic cell death[35]. The precursor form of IL-1α is upregulated and subsequently released from dying cells following hypoxia[36]. IL-1α released by necrotic hepatocytes contributes to compensatory proliferation and carcinogenesis[36]. IL-1α exists not only as a soluble form whose maturation and secretion is inflammasome and caspase-1 dependent[37], but also as a cell-surface protein that is able to activate IL-1 receptor-like 1 on target cells such as T-cells and endothelial cells and potentiates induction of other cytokines[38]. While the secreted form of IL-1α is highly pro-inflammatory in the tumor microenvironment and involved in tumor growth and invasiveness, its membrane form favors anti-tumor immunity, and leads to reduced tumor growth and invasiveness[38]. IL-33 is another cytokine released by necrotic cells and by a variety of tissue types under stress conditions[39]. Endogenous IL-33 expression is increased in tumor tissue and contributes to cancer progression[40–42]. IL-33 upregulation in tumor also correlates with increased expression of target receptor complex IL-1 receptor-like 1 in stromal cells[41, 42], reflecting a paracrine effect of IL-33 as a result of crosstalk between tumor cells and surrounding stroma.

In addition to DAMPs secreted within tumors, it is also conceivable that DAMP secretion from cells in the tumor microenvironment can modulate tumor biology and development. However, this area requires further investigation.

While there is ample evidence for DAMP release in multiple settings, much of the current data is based on cell lines and animal models. Further studies are required to understand DAMP release in human cancer patients, to what degree therapeutic inventions alter DAMP release and whether DAMP levels correlate with therapeutic prognosis or clinical outcome. In systemic therapies, it is likely that DAMPs are not only released from tumors but that a large proportion of DAMPs are derived from other cell types that are typically affected by chemotherapy or irradiation such as intestinal epithelia. Hence, DAMPs from these cells rather than tumor-derived DAMPs might also affect inflammation and immune responses.

2. Contribution of DAMPs to tumor promotion via inflammation or immunosuppression

Whereas acute inflammation is often beneficial for the host and an essential component of pathogen defense and tissue repair, failure to eliminate the causative agent leads to chronic unresolved inflammation that promotes mal-adaptive wound healing and increased risk to develop cancer as demonstrated in animal models[13, 14, 43] and humans[13]. Mechanistically, inflammation predisposes to malignant transformation via multiple mechanisms, including (i) genetic damage caused by inflammation-associated reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI), (ii) promotion of proliferation via cytokine-induced growth factors, and (iii) resistance to cell death via activation of anti-apoptotic cell death pathways such as NF-κB. Accordingly, the most prevalent conditions predisposing to cancer all have significant inflammatory components, such as chronic infections (i.e., *H. pylori*, HBV, HCV, HPV), exposure to inhalative pathogens (including cigarette smoke, asbestos, silica) as well as obesity[13, 44, 45]. In addition to inflammatory conditions that promote the

development of tumors, inflammation is also an essential component of established tumors. Of note, inflammation is not merely an epiphenomenon but an essential driver of tumor growth, whose significance for the progression of malignant disease is highlighted by their emergence as a novel "hallmark of cancer"[46]. The role of tumor-associated inflammation is highly context- and stage- and tumor-specific. While inflammation in early stages may contribute to anti-tumor responses, immune cell exhaustion and loss of neoantigens after initially successful immunoediting may switch inflammation into a tumor-promoting response once anti-tumor immunity has started failing[47, 48]. DAMPs including HMGB1, S100 and heat shock proteins, act via potent PRRs that are also employed by PAMPs such as Toll-like receptors (TLRs), formyl peptide receptor (FPR), C-type lectins and the receptor for advanced glycation endproducts (RAGE). These receptors activate a shared set of inflammatory pathways, including NF-κB, p38, ERK, inflammasome assembly and IL-1β and IL-18 release, as well as secretion of IL-6, TNF, LT-β, IFNγ and TGF-β, and promote the recruitment of inflammatory cells. As such, IL-1, IL-6 and LT-β are well-known promoters of carcinogenesis[14, 43, 49, 50]; recent evidence suggests that recruited inflammatory cells, in particular "ectopic lymphoid structures" – which are often in close proximity to damaged tissue – promote the development of cancer[51]. Not only is there a strong correlation between DAMP expression and carcinogenesis in multiple tumors, but a plethora of DAMPs have been implicated in promoting inflammation and tumor development both in early stages of carcinogenesis as well as in established tumors (Fig. 1; Table 1). In addition to promoting tumor growth via increased inflammation, there is accumulating evidence that multiple DAMPs also exert immunosuppressive effects that ultimately promote the development or progression of tumors (Fig. 1; Table 1).

HMGB1

HMGB1 is overexpressed in precancerous states such as liver cirrhosis and gastric dysplasia[52, 53] as well as in a wide range of tumors[54–58] and may trigger a number of inflammatory responses that promote tumor development and/or progression. HMGB1 triggers the recruitment of neutrophils, subsequent inflammation and amplification of injury in multiple injury models[59, 60]. Ablation of HMGB1 receptor RAGE suppresses carcinogenesis in multiple cancer models, including inflammation-induced liver and skin cancer as well as a xenotransplant glioma model[61–63]. As such, HMGB1 promotes the recruitment and activation of intratumoral T cells in prostate cancer, which in turn recruit tumor-promoting macrophages[64]. Moreover, HMGB1 promotes the growth of hepatocellular carcinoma in concert with mitochondrial DNA via activation of TLR9[31]. TLR4, another receptor for HMGB1, is also expressed by tumor cells; activation of the TLR4 pathway has been associated with tumor cell survival, chemoresistance and tumor progression and metastasis[65]. Of note, the HMGB1-TLR4/RAGE pathway has recently been involved in chemoresistance to docetaxel by inducing the secretory/cytoplasmic clusterin in prostate tumor cells, a potent anti-apoptotic protein that mediates BAX sequestration, preventing caspase 3 activation[66]. Chemotherapy-induced release of HMGB1 from necrotic colon cancer cells enhances the growth and metastasis of remnant cancer cells through RAGE[67] while blockade of the HMGB1-RAGE axis inhibits tumor growth and metastasis[63] and enhances sensitivity to chemotherapy[68]. Moreover, HMGB1 released from hypoxic cells

triggers endothelial cell proliferation *in vitro* and neoangiogenesis *in vivo*[69], and expression levels of HMGB1 in tumors are associated with invasion and metastasis[53].

Interactions between HMGB1 and TIM-3, expressed on DC, result in suppression of the therapeutic efficacy and of DNA vaccination and chemotherapy by decreasing immunogenicity of nucleic acids released from dying tumor cells[70]. Hence, HMGB1 may not only promote carcinogenesis via the activation of inflammatory pathway but also through immunosuppressive pathways.

ATP and adenosine

Although there are unusually high concentrations of extracellular ATP in the tumor interstitium as well as increased expression levels of the ATP receptor P2X7R on a variety of human cancers[18, 71], there is only limited evidence in supporting their role in tumor promotion. Although P2X7 promotes inflammation, largely mediated by activation of the inflammasome[72], and modulates myeloid-derived suppressor cell (MDSC) immunosuppressive functions[73], the majority of studies show a protective role (see next section). The finding that P2X7R-deficiency exacerbated tumor development in a colitis-associated colon cancer model despite decreased inflammation[74] suggests only a limited role in P2X7R-mediated inflammation in promoting carcinogenesis. Adenosine is a potent anti-inflammatory DAMP that acts on a variety of cell types and contributes to limiting inflammatory response following injury. Increased adenosine levels in the tumor microenvironment contribute to tumor progression via suppression of T cells and natural killer (NK) cells[19]. Stimulation of A2A receptor decreases maturation and cytotoxic function of NK cells, leading to promotion of metastasis[75]. Moreover, regulatory T (Treg) cells express ectonucleotidases CD39 and CD73 in a variety of tumors[19, 76], resulting in increased generation of pericellular adenosine and A2A receptor-mediated inhibition of effector T cells. CD73 is also expressed on tumor cells or stroma, which further increases adenosine levels and contributes to immune evasion by suppressing T cell recruitment and activation as well as chemoresistance to doxorubicin in an A2A-dependent manner[76–78]. Accordingly, blockade of CD73 inhibits breast tumor growth and metastasis[79] and increases doxorubicin-mediated anti-tumor immune response[78]. Moreover, a large number of studies have shown that adenosine triggers tumor proliferation via A1 and A3 receptors[19], suggesting that this pathway may contribute to tumor progression. Moreover, adenosine promotes chemotaxis and metastasis via A2B receptors[79].

S100 proteins

Dysregulated expression of various members of the S100 protein family has been observed in various cancers, with tumor-stage and –subtype specific expression profiles. Similarly to HMGB1, S100A8/A9 and S100A12 circulating levels are upregulated in a number of chronic inflammatory diseases and types of tumors and strongly correlate with disease course and/or severity[34]. In addition, the S100A8/A9-RAGE axis links inflammation and tumor promotion through activation of MAPK and NF-κB pathways[61, 80]. S100 proteins have been ascribed with diverse DAMP functions following release from necrotic cells, mostly through interaction with RAGE, although interaction with TLR4 has been demonstrated in other settings[60, 81]. Interference with their expression or signaling pathways

has subsequently revealed a complex role for the various S100 proteins in the growth and dissemination of established tumors, with effects both on cancer cell growth as well as on concomitant inflammation[22]. As such, the expression S100A8 and S100A9 is induced by distant primary tumors, resulting in the attraction of myeloid cells in the premetastatic lung[82]. This is mediated by the induction of S100A8- and S100A9-induced production of SAA3, which in turn activated TLR4 and facilitated metastasis[83]. In addition, S100A8 and S100A9 act directly on tumor cells, activating p38 MAPK, thereby promoting tumor cell migration[82]. Similarly, it has been shown that low concentrations of extracellular S100A8/9 also enhance NF-κB activation in tumor cells and promotes their growth through interactions with RAGE[84]. S100A4 expression is significantly increased in prostate cancer cell lines compared to normal prostate epithelial cells, and expression correlates with increased tumor grade[85]. A causative relationship between S100A4 expression and tumor progression has been demonstrated in colon cancer cells, where pharmacologic targeting of S100A4 via the anti-helmintic niclosamide profoundly inhibited growth and metastatic spread[86]. S100A4, however, apparently exhibits both tumor cell-intrinsic as well as –extrinsic effects, as demonstrated by the ability of S100A4 from metastases-associated stroma to bind to RAGE on tumor cells, leading to the secretion of paracrine factors and pro-inflammatory cytokines such as IL-8, CCL2, IL-6 and IL-1β, which in turn promote angiogenesis and pro-tumor immune responses[87]. Accordingly, both intracellular and extracellular S100A4 may represent promising therapeutic targets to prevent progression of neoplastic diseases.

In addition to promoting inflammation, recruitment of macrophages and tumor migration, S100 proteins also affect anti-tumor immune responses. As such, S100A9 enhances the production of myeloid-derived suppressor cells, thereby suppression anti-tumor responses. S100A9-deficient mice rejected implanted tumors, which was reversed by administration of wild-type MDSCs from tumor-bearing mice to S100A9-deficient mice[88]. Notably, RAGE null mice exhibit reduced tumor growth in experimental skin and colon cancers[61, 62, 89], and display reduced numbers of MDSC in tumor stroma, pointing at a central role for RAGE in the mediation of S100A8/A9-mediated MDSC recruitment[90, 91].

Uric acid

Dying cells release their intracellular uric acid stores, and additional uric acid is generated *post mortem* during enzymatic degradation of nucleic acids. Extracellular uric acid triggers inflammatory responses to cell death, possibly through TLR4-mediated NLRP3 inflammasome activation[92], by mediating neutrophil activation[93] as well as DC maturation and T cell differentiation[94]. Moreover, cancer cells themselves respond to uric acid by increasing migratory activity[95]. Accordingly, elevated uric acid levels in patients have been associated with an excess cancer risk[96]. However, uric acid released from tumors subject to chemotherapy or immune rejection accelerates tumor regression[97].

3. Contribution of DAMPs to tumor inhibition/rejection via immunogenic cell death and other mechanisms

Physiological cell death, such as apoptosis, has long been considered non- or low-inflammatory due to the rapid removal of apoptotic cells by phagocytic cells, whereas pathological cell death, induced by physicochemical stress or noxious stimuli, such as necrosis, necroptosis and pyroptosis, has been described as inherently immunogenic and highly inflammatory. Since cancer therapies often induce cell death via apoptosis and additionally can be immunosuppressive either on their own or in combination with the commonly co-administered corticosteroids, the concept that tumor cell death triggered by cytostatic therapies might be immunogenic has long been ignored[98]. However, this traditional perspective of cell death has been challenged by the finding that in response to specific anti-cancer agents, tumor cells can undergo an immunogenic cell death (ICD) that combines modalities of apoptosis with the emission of DAMPs, fostering a potent, therapeutic reinforcing anti-tumor immune response (Fig 2). Moreover, tumor cell death is not selectively apoptotic as other death modalities including necrosis and necroptosis are also potently induced by cytostatic therapies and necrosis is even commonly found in untreated tumors, often visible as necrotic tumor center[17, 25, 26]. Although the contribution of non-apoptotic forms of cell death including necrosis, necroptosis and pyroptosis to ICD is not as well characterized, it is likely that non-apoptotic cell death commonly occurs in anti-cancer therapy strategies such as chemotherapy and irradiation[17, 25, 26]. There is accumulating evidence that DAMPs exert a key role in ICD. ICD strongly relies on the induction of an ER stress response triggered or accentuated by ROS production[6, 99]. The combined action of ER stress and ROS promotes the activation of DAMP signaling pathways, involving the pre-apoptotic exposure of the ER chaperone CRT on the cell surface (ecto-CRT)[5], early apoptotic secretion of ATP[100], and post-apoptotic release of HMGB1[101]. Engagement of these DAMPs with various target receptors present on immune cells, leads to the elicitation of a potent anti-tumor immunity (Fig. 2; Table 1). Several studies demonstrated that interfering with the emission of these DAMPs compromised the anti-tumor immune response[5, 23, 100], providing evidence for its critical role in shaping cancer cell immunogenicity. However, a recent study using spontaneous mammary tumor models demonstrated that the adaptive immune system is dispensable for the therapeutic efficacy of oxaliplatin, doxorubicin and cisplatin[102], raising concerns about experimental models used for ICD studies. In fact, most landmark studies on ICD rely on functional data from cell line-based models[5, 6, 70, 100, 103–105]. Transplanted cell lines are likely to differ substantially in their genetic profile to endogenously arising tumors and thus may induce immune responses that cannot be triggered by endogenously arising tumors. In addition to more profoundly altered genetic profiles, endogenous tumors undergo constant immunoediting[106], whereas transplanted cell lines lack this selection and are most likely much more immunogenic due to a higher load of tumor antigens to which the host immune system can respond. Some of the concerns are alleviated the inclusion of human data in recent studies, showing poorer survival in patients with loss of function of FPR1[105] or more rapid development of metastasis in patients with loss of function of P2X7R[103]. Additional studies in models with endogenously arising tumors would further confirm the relevance of ICD as well as the contribution of DAMPs to this process.

Calreticulin

CRT is one of the best-characterized mediators of ICD. CRT translocation triggered by chemotherapy and UVC irradiation relies on PERK-mediated eIF2α phosphorylation followed by capase-8 mediated BAP31-dependent activation of BAX/BAK proteins[99]. However, eIF2α phosphorylation and caspase-8 are dispensable for photodynamic therapy (PDT)-induced ecto-CRT exposure[6]. Ecto-CRT functions as a pro-phagocytic signal for DC[5] and promotes the IL-6 and TNF-mediated priming of the T helper 17 (Th17) cells through scavenger receptor CD91[107]. The presence of ecto-CRT has also been demonstrated in immune cells, including DC, where it was found to interact with NY-ESO-1, a tumor associated antigen with distinctively strong immunogenicity[108], confirming its role in linking tumor and host immune response. Of note, the recombinant N-terminal fragment of CRT was sufficient to stimulate B cells and macrophage activation[109], arguing for a potent immunostimulatory role of the soluble form of CRT. Interestingly, resistance to anti-cancer vaccination induced by ICD was associated with a defect in ecto-CRT exposure resulting from low endogenous CRT protein levels and rescued by exogenous reconstitution of ecto-CRT[110]. In the same study, CRT expression was a predictive biomarker of anticancer therapy response in cancer patients and a potential regulator of phagocytosis in tumors in ICD clinical settings[110]. Although necessary, CRT translocation is not sufficient to elicit an anti-tumor response, which relies on additional signaling pathways involved in antigen processing and presentation and immune cells polarization.

ATP and adenosine

Extracellular ATP is a critical effector in ICD[103]. Similarly to CRT translocation, ATP release seems to be dependent on cell death stimulus and modalities. PTD-induced, pre-apoptotic release of ATP relies on the overlapping classical secretory pathway as well as PERK-regulated secretory and PI3 kinase-dependent extracellular trafficking pathways and is independent of BAX/BAK. Early apoptotic secretion of ATP has been shown to be pannexin 1 hemichannels-dependent following UVC irradiation[111] and autophagy-dependent in dying cells undergoing chemotherapy (anthracyclines and oxaliplatin)[6, 100]. Once released from the dying cancer cells, ATP displays a dual effect, both acting as a chemotaxis inducer and activator of the inflammasome pathway depending on its extracellular concentration[112]. ATP released by apoptotic cells has been shown to promote P2Y2R dependent-phagocytic clearance[113] and P2X7R-dependent activation of the NLRP3 inflammasome by chemotherapeutic agents. The subsequent activation of caspase-1 then leads to the secretion of IL-1β and polarization of IFNγ-producing CD8+ T cells[100, 103]. ATP from dying cancer cells attracts myeloid cells to the site of cell death[104], and ATP receptors P2Y2R and P2X7R stimulate the recruitment of DC and inflammatory cells into the tumor stroma as well as the maturation of T cells into the cytotoxic CD8+ phenotype[103, 104, 114]. P2X7R, which has a low affinity for ATP, is critical to support antitumor immune response and restrict tumor progression specially via its expression on host hematopoietic cells[114]. Ivermectin, an anti-parasitic drug, has been shown to display anti-tumor properties *in vivo*, due to its ability to stimulate P2X4R/P2X7R/Pannexin-1 signaling and to promote a novel form of cancer cell death involving a combination of apoptosis and highly inflammatory regulated necrosis, consistent with pyroptosis[115]. Noteworthy, adenosine, resulting from ATP hydrolysis by the ectoenzymes CD73 and CD39

exerts effect that are often opposite to those of ATP (see details in previous section), such as the promotion of an immunosuppressive environment via A2A receptors[76, 116, 117] as well as chemotaxis and metastasis via A2B receptors[79]. However, adenosine can also induce tumor cell death, via A1, A2A, A2B and A3 receptors[19118], thereby additionally contributing to limit tumor growth (Fig 2). Therefore, the kinetics of ATP release and conversion to adenosine, as well as the large number of receptors for ATP and adenosine need to be taken into consideration when targeting this system for ICD induction.

Annexin A1/FPR1

Formyl peptide receptor 1 (FPR1) is a PRR that – besides recognizing N-formylated peptides from bacteria – also interacts with several DAMPs including annexin A1. Recent studies have shown that a single nucleotide polymorphism, which suppresses FPR1 signaling, was associated with reduced survival in patients receiving adjuvant chemotherapy for breast or colorectal cancer[105]. In experimental models, FPR1 expression on the host and expression of FPR1 ligand annexin A1 on tumor cells were required for chemotherapy-induced reduction of tumor growth. Likewise, treatment with FPR1 antagonist cyclosporine H also abolished anti-cancer effects of chemotherapy[105]. Mechanistically, FPR1 was dispensable for the recruitment of DC to the tumor bed, but was required for DC to come into close proximity to dying cancer cells, take up tumor-associated antigens and cross-present them to T cells[105].

HMGB1

Although it was initially thought that HMGB1 release primarily occurred following necrosis, several studies also pointed out that HMGB1 release could also be associated with apoptosis, specifically during secondary necrosis. Post-apoptotic release of HMGB1, as triggered by radiotherapy or chemotherapy (anthracyclines), enhances DC-mediated antigen presentation via TLR4[23]. In this context, HMGB1 acts as a critical mediator of the TLR4-dependent processing of exogenous tumor antigens by DC but does not promote DC migration and maturation which primarily involves the HMGB1-RAGE axis[119]. HMGB1 stimulates DC maturation through RAGE and leads to T-helper 1 polarization[120]. Interestingly, RAGE-mediated HMGB1 endocytosis has recently been described as a trigger of pyroptosis in macrophages[121], which could represent a potential feedback mechanism promoting anti-tumor immunity during ICD. Although chemotherapy-induced HMGB1-TLR4 axis signaling has mainly been involved in eliciting anti-tumor responses, HMGB1 has also been showed to foster an immunosuppressive and pro-tumor environment (see previous section; Fig. 1, Table 1), which could negatively impact the outcome of anti-cancer therapies. The opposites roles of HMGB1 in tumorigenesis and ICD following anti-cancer therapies might be attributable to its redox status that defines its molecular interaction and activities[122, 123], and plays a key role in cell fate regulation[124, 125]. Indeed, reducible HMGB1 induces Rage/Beclin1-dependent autophagy in cancer cells, promoting tumor resistance to chemotherapeutic agents or radiotherapy, whereas oxidized HMGB1 enhances the cytotoxicity of these chemotherapeutics and triggers apoptosis mediated by the caspase-9/-3 intrinsic pathway[124]. Of note, the extracellular milieu, known to be oxidative under physiologic conditions, is altered and highly variable under pathologic conditions, such as cancer, as evidenced by *in vitro* culture of different cancer cell lines[126]. *In vivo*, the tumor

microenvironment tends to be pro-oxidative which would diminish the pro-inflammatory properties of HMGB1 via oxidation-mediated inactivation[122, 123, 127].

Finally, loss of membrane integrity occurring during primary or secondary necrosis leads to the release of uric acid, DNA, ATP, and N-formyl peptides that can participate and reinforce the anti-tumor response. As such, DNA released after chemotherapy-induced cell death[70] can efficiently stimulate an antigen-specific anti-tumor immune response, and uric acid enhances tumor immune rejection[97].

4. Tumor-specific DAMPs versus DAMPs from non-tumor cells following cytostatic therapy

The most profound release of DAMPs occurs in response to cytostatic therapies. However, these therapies are by no means tumor-specific and induce cell death in rapidly proliferating cells in many organs including bone marrow, gastrointestinal tract and hair follicles. Hence, it is likely that a significant proportion of DAMPs are released from non-tumor compartments in response to cytostatic therapies. Additional studies are required to determine whether DAMPs from healthy cells in these compartments modulate inflammatory and immune responses including ICD in the setting of cytostatic therapies.

Another key point that has not been sufficient addressed is the potential role of yet unknown tumor cell-specific DAMPs. The majority of studies on the role of DAMPs in tumors have been based on DAMPs discovered in models of non-malignant disease. Due to the profound aberrations of a wide range of pathways in tumor cells, tumor-specific DAMPs could be generated by a number of mechanisms, including posttranslational alterations and alterations in the secretion of mediators that are typically retained within healthy cells. In this regard, tumor-specific DAMPs could also be a cargo of exosomes, whose secretion is commonly upregulated in tumor cells.

5. Exploiting DAMPs for tumor prevention or anti-tumor therapy

It is conceivable that DAMPs can be targeted in different stages of carcinogenesis. Considering that constant cell death favors tumor development in organs such as the liver, one could envision blocking DAMP signaling as tumor-preventative strategy. On the other hand, the recently established key role of DAMPs in the immune system's response to tumors, in particular in the setting of anti-tumor therapies, suggests that activating DAMPs signaling pathways might be exploited for anti-tumor therapies, analogous to PRR-mediated activation of anti-tumor pathways by "Coley's toxin". However, this view is likely to be simplistic as PRR-induced immunostimulatory signals may not only fail in chronic setting but even get "hijacked" by the tumor, resulting in tumor-promoting inflammation rather than an efficient anti-tumor response in the long-run. For this reason, it appears more promising to activate DAMP signaling pathways in conjunction with cystostatic therapies as well as therapies that prevent immune exhaustion such as checkpoint inhibitors. This might ensure continuous activation of anti-tumor responses and ICD, and might be particular appealing in settings when tumor mass is small and release of DAMPs minimal, e.g. as a type of adjuvant therapy after curative resection. In this regard, a recent study has identified FPR1 as

determinant of chemotherapy-induced immunity and survival in adjuvant setting. Although these data are promising and may open new possibilities for treatment, we still need a better understanding of the role of specific DAMPs and their cellular targets as these responses are likely to be mediated by multiple DAMPs in complex signaling networks. It is likely that contribution of DAMPs and their receptors to carcinogenesis and ICD are organ-, tumor- and context-specific, and that key DAMPs in this setting are yet-to-be identified molecules or DAMPs with specific post-translational modifications. Moreover, it is conceivable that immuno-suppressive effects of chemotherapy may dominate in some organs as suggested by studies that demonstrated chemotherapy-induced plasma cell recruitment and subsequent plasma cell-mediated inhibition of chemotherapeutic efficacy[128]. Finally, it is also likely that DAMPs shape the tumor microenvironment which in turn provides essential support for the tumor[129]. Hence, targeting select DAMPs that contribute to a tumor-promoting microenvironment may be beneficial. In summary, further understanding of the diverse roles of DAMPs in cancer is required before DAMPs can be exploited for therapeutic strategies, and it is likely that these therapeutic approaches might incorporate both activation and inhibition of DAMP signaling pathways.

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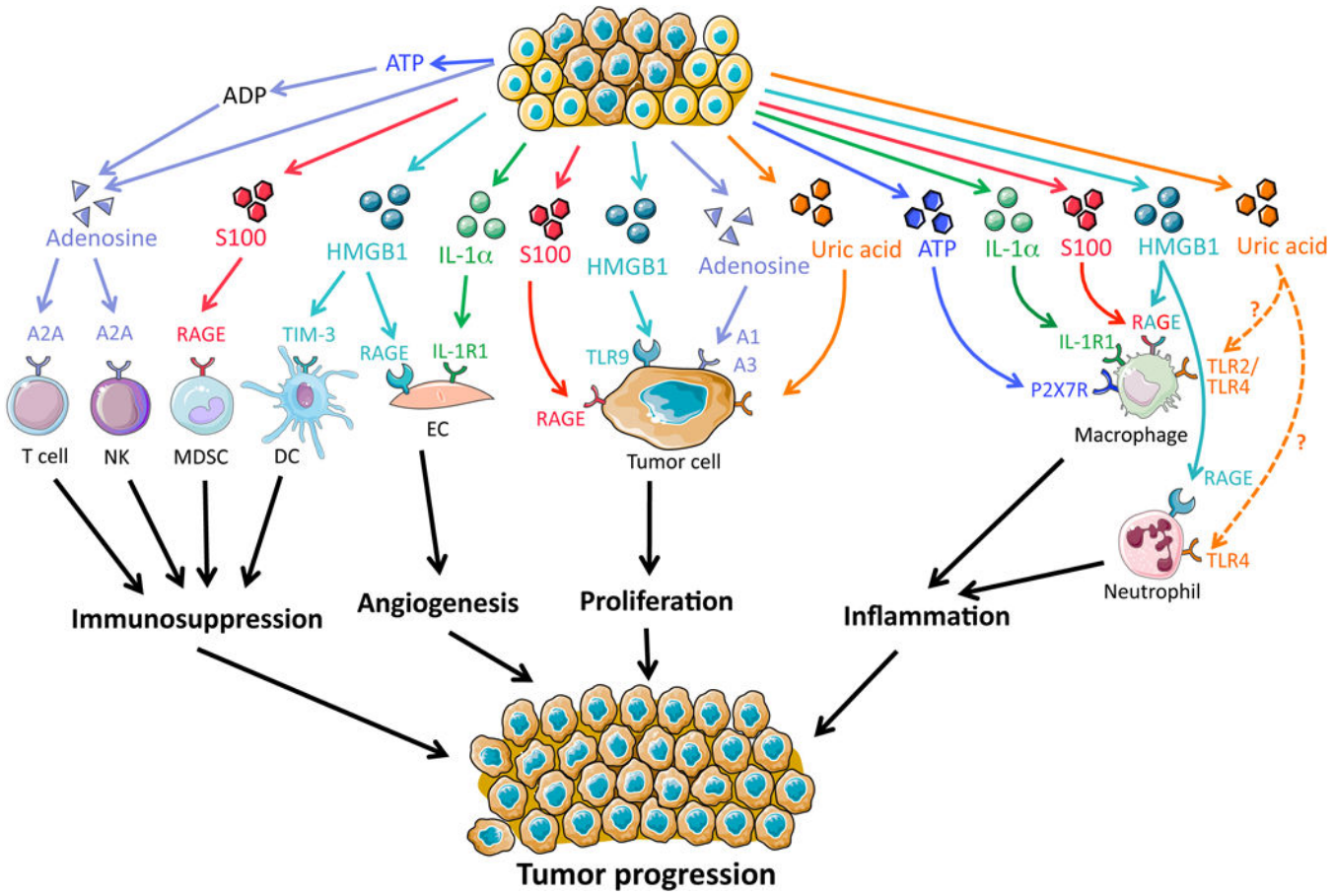

Fig 1. DAMPs mediate tumor progression

Cellular release of DAMPs such as uric acid, HMGB1, S100 proteins, IL-1α and adenosine can promote tumor progression via distinct mechanisms and target cells. Adenosine and HMGB1 may contribute to immunosuppression, HMGB1 and IL-1α to angiogenesis; uric acid, HMGB1, S100 proteins and adenosine to tumor cell proliferation; and ATP, IL-1α, S100 proteins, HMGB1 and uric acid to inflammation. NK, natural killer cell; MDSC, myeloid-derived suppressor cell; DC, dendritic cell; EC, endothelial cell.

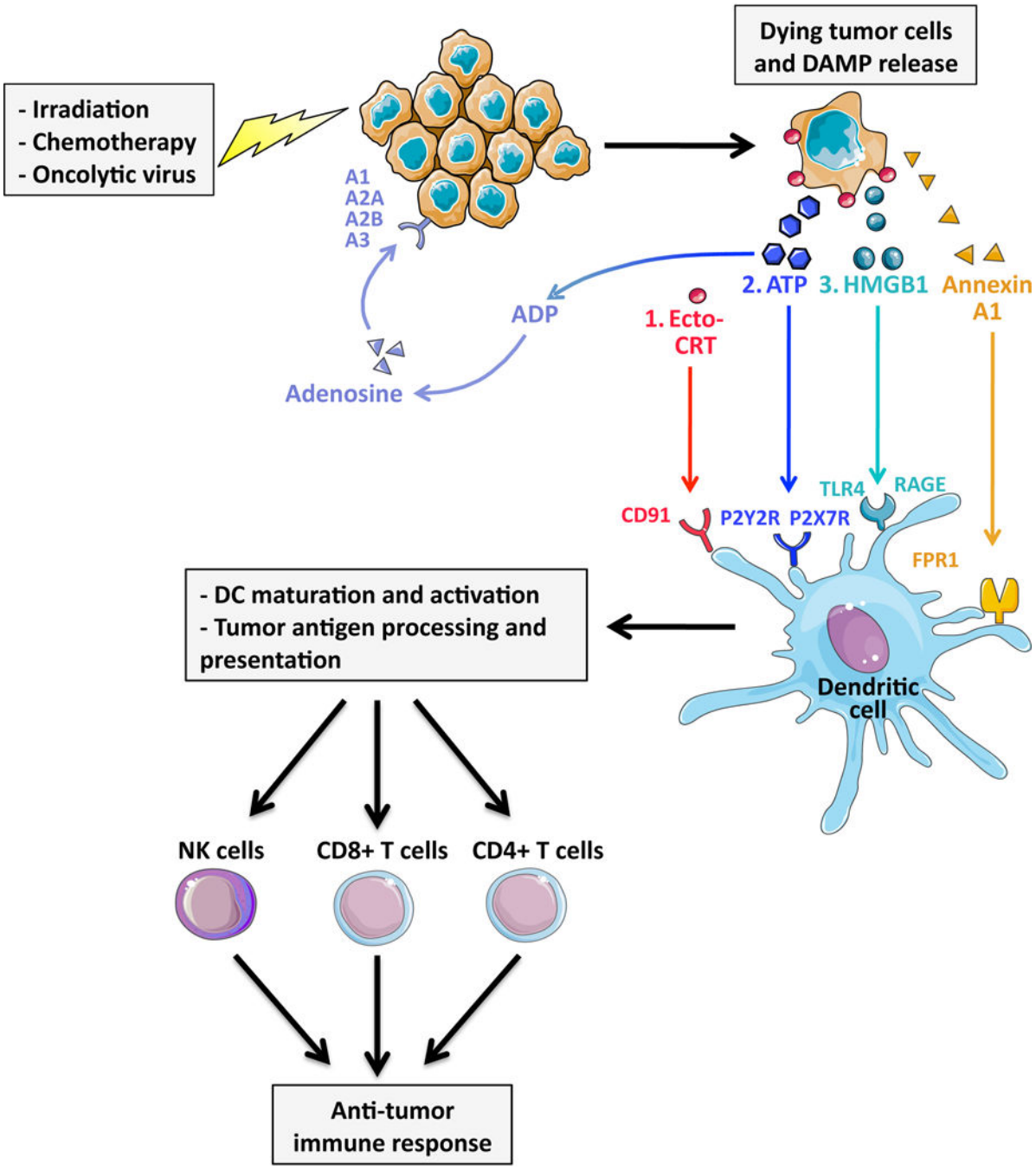

Fig 2. Contribution of DAMPs to tumor rejection via ICD

Immunogenic cell death (ICD), induced by various anti-cancer therapies strongly relies on the activation of DAMP signaling pathways. Following exposure irradiation, treatment with select chemotherapeutic agents and or infections with oncolytic viruses, tumor cells release DAMPs in the following order: 1. pre-apoptotic exposure of the ER chaperone calreticulin on the cell surface (ecto-CRT); 2. early apoptotic secretion of ATP; 3. post-apoptotic release of HMGB1. These DAMPs engage their respective receptors including CD91, P2X7R, P2Y2R, RAGE and TLR4 on the surface of dendritic cells (DC), triggering DC engulfment

of dying cells, tumor antigen processing and presentation. In addition, Annexin A1, via its receptor FPR1, is required to bring DC into close proximity to dying tumor cells. DC maturation and activation ultimately foster potent anti-tumor responses via recruitment and activation of CD4+ and CD8+ T cells and natural killer (NK) cells.

Table 1

DAMP	Receptor	Tumor	Main effects	Target cell	Effect on Tumor	Ref
Adenosine	A1	Breast cancer	Cell proliferation	Tumor cells	Tumor growth	19
		Glioblastoma multiforme	Anti-proliferative/pro-apoptotic effect	Cancer stem cells	Chemotherapy sensitivity	118
	A2A		Immunosuppression	Treg	Likely to promote tumors	76
			Treg expansion, immunosuppression	T cells and Treg	Likely to promote tumors	117
			Inhibition of cytokines and chemokines release.	Teff and Treg	Likely to promote tumors	116
		Lewis Lung carcinoma	Accumulation of intratumoral granulocytic MDSC	Hematopoietic cells	Tumor promotion	130
		Lewis lung carcinoma	Suppression of NK cell maturation and activation	NK cells	Tumor immune evasion	19
	A2B	Breast cancer	Tumor cell migration and metastasis	Tumor cells	Tumor promotion and metastasis	79
		Ovarian cancer Melanoma, lymphoma	Decreased T cell infiltration	T cells	Tumor immune evasion	77
		Glioblastoma multiforme	Anti-proliferative/pro-apoptotic effect	Cancer stem cells	Chemotherapy sensitivity	118
	A3	Breast cancer, Colorectal cancer melanoma, lymphoma	Proliferation	Tumor cells	Tumor promotion	19
ATP	P2X7	Sarcoma, lymphoma, colon cancer	NLRP3 inflammasome activation, cells recruitment, priming adaptive immune response, polarization CD8+ T cells	DC	Anti-tumor immune response, Tumor inhibition	103
		Neuroblastoma	Immunosuppression	Monocytic MDSC	Tumor immune evasion	73
	P2Y2	Breast cancer, Leukemia	Recruitment, immunosuppression	DC, Macrophages	Anti-tumor immune response, Tumor inhibition	113
		Sarcoma, lymphoma, prostate cancer	Recruitment and differentiation	Myeloid cells	Anti-tumor immune response	104
HMGB1	?	Prostate cancer	Priming adaptive immune response Proliferation	T cells	Tumor promotion	64
	?		Endothelial cell migration and sprouting	Endothelial cells	Likely to promote tumors	69
	RAGE?	Malignant mesothelioma	Migration and proliferation	Tumor cells	Tumor promotion	33
	RAGE	Hepatocellular carcinoma	Progenitor cell proliferation	Progenitor cells	Likely to promote tumors	62
			Neutrophil recruitment, injury amplification	Neutrophils	Not shown	59
	RAGE		DC maturation, clonal expansion, T cells activation, Th1 polarization	DC	Not shown	119
		Colon carcinoma Lung carcinoma	Tumor regrowth and metastasis of remnant cancer cells following chemotherapy	Tumor cells	Tumor regrowth and metastasis	67
		Pancreatic adenocarcinoma	Increased autophagy, decreased apoptosis	Tumor cells	Tumor survival (chemotherapy resistance)	68
	RAGE/TLR4	Prostate cancer	Induction of secretory/cytoplasmic clusterin, cell death inhibition	Tumor cells	Tumor survival (chemotherapy resistance)	66

DAMP	Receptor	Tumor	Main effects	Target cell	Effect on Tumor	Ref
	TLR4	Mammary carcinoma, fibrosarcoma, lymphoma, colon carcinoma, osteosarcoma	Tumor Antigen processing and presentation	DC	Anti-tumor immune response	101
	TLR9	Hepatocellular carcinoma	Proliferation, angiogenesis	Hypoxic tumor cells	Tumor progression	31
	TIM-3	Melanoma, Colon carcinoma, Lewis lung carcinoma	Decreased immunogenicity of nucleic acids	DC	Decreased tumor immune rejection	70
Annexin A1	Formyl peptide receptor (FPR)	Breast carcinoma, Lung carcinoma, Fibrosarcoma,	Chemotherapy-induced antitumoral T cell response	DC	Chemotherapy-induced reduction of tumor growth	105
Calreticulin	Unknown	Colon carcinoma	Tumor cell uptake by dendritic cells and chemotherapy-induced anti-tumoral immune response	DC	Chemotherapy-induced reduction of tumor growth	5
		Lymphoma	IL-6 and TNF-mediated Th17 priming	APC	Anti-tumor immune response (not shown)	107
S100A8/9	RAGE	Breast carcinoma, Fibrosarcoma, Neuroblastoma	NF-κB activation, cell growth	Tumor cells	Tumor growth	84
		Colon carcinoma Colorectal adenocarcinoma	Myeloid cells infiltration, inflammation, protumorigenic gene activation	Tumor cells	Tumor promotion and progression	80
		Skin cancer	Infiltration, inflammation, epidermal hyperplasia	Immune cells	Tumor promotion and progression	61
S100A4	?	Melanoma	Secretion of paracrine factors and pro-inflammatory cytokines promoting angiogenesis and pro-tumor immune response	Tumor cells	Metastasis	87
		Colon cancer	Metastasis, invasion, proliferation	Tumor cells	Metastasis and tumor progression	86
Uric acid	TLR2/TLR4		NLRP3 inflammasome activation	Macrophage	Not shown	92
	?		Neutrophil recruitment, inflammation	Neutrophil	Not shown	93
	?	Breast carcinoma	Migration	Tumor cells	Likely to promote tumors	95
	?	Leukemia	Recruitment	Monocytes/macrophages	Anti-tumor immune response	97
IL-1	IL-1R1		Cell activation, cytokine release	Endothelial cells, T cells Macrophages	Tumor invasiveness Tumor-promoting inflammation	38
IL-33	IL-1R1	Breast carcinoma	Intratumoral accumulation of immunosuppressive cells, decreased innate antitumoral immunity Intratumoral cell proliferation Angiogenesis	MDSC, NK, DC, macrophages Tumor cells Endothelial cells	Tumor progression	40
		Colorectal cancer	Cell activation, proliferation, apoptosis, angiogenesis	Stromal cell types, subepithelial myofibroblasts and mast cells	Tumor growth and progression	41
		Colorectal Cancer	Invasion, growth, metastasis	Tumor cells	Tumor growth and progression	42