Seminars in Cancer Biology 22 (2012) 23–32

Contents lists available at SciVerse ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

Inflammation and immune surveillance in cancer

Melvyn T. Chow[a,b], Andreas Möller[b,c,1], Mark J. Smyth[a,b,*,1]

[a] Cancer Immunology Program, Peter MacCallum Cancer Centre, St. Andrews Place, East Melbourne, Victoria 3002, Australia
[b] Sir Peter MacCallum Department of Oncology and Department of Pathology, University of Melbourne, Parkville, Victoria 3010, Australia
[c] Cancer Genomics and Genetics Laboratory, Peter MacCallum Cancer Centre, St. Andrews Place, East Melbourne, Victoria 3002, Australia

ARTICLE INFO

Keywords:
Inflammation
Immunoediting
Danger signal
Toll-like receptor
Inflammasome

ABSTRACT

Chronic inflammation is a risk factor for tumor development. However, understanding the effect of the immune system on tumor development has only been significantly advanced over the past two decades. We now appreciate that the immune system, in addition to tumor-suppressive function by eliminating nascent transformed tumor cells, can also exert selection pressure on tumor cells and facilitate tumor growth by providing a favorable tumor microenvironment. Yet, the distinctions between tumor-promoting inflammation and tumor-suppressive immunity are still not clear due to the dual role of some cytokines and other molecules in the immune system. The danger signal hypothesis has shaped our view of the role of immunity in cancer development, but still little is known about the exact role of danger signal receptors in cancer progression. In this review, we introduce the processes of cancer immunoediting and inflammation-induced cancer and discuss what is currently known about the role of danger signal receptors in cancer development and progression.

1. Introduction

The capability and contribution of the immune system to effectively control the cancer growth has been a controversial topic for many years. Paul Ehrlich, in 1909, was one of the first to propose the concept that the immune system has a critical role in protecting the host from cancer [1]. He reasoned that otherwise cancer would occur at a much higher frequency in long-lived animals. However, this hypothesis was not proven experimentally due to the inadequacy of experimental tools and knowledge of detailed immunology at the time. Around the middle of the twentieth century the dawning, and then subsequent rapid development, of cellular immunology encouraged Burnet and Thomas to architect the "cancer immunosurveillance" hypothesis [2,3]. Subsequent attempts to prove its validity – to show that a host with an impaired immune system would be more susceptible to tumors – were limited to approaches using virus-induced tumors or chemical-induced tumors [4–7]. It was debated whether the controversial findings could be ascribed to virus-mediated transformation as a result of defective control of viral infection rather than as a consequence of a direct effect of the impaired immune response against the cancer cells. Subsequent work of Osias Stutman and colleagues further fueled this debate. Stutman used the CBA/H nude mouse strain, the most congenitally immunodeficient mice available at the time. He found that the development of methylcholantherene (MCA)-induced sarcomas was not different between these nude mice and wild-type mice [8]. On the basis of these findings, enthusiasm for the validity of the immunosurveillance hypothesis waned and eventually led to the abandonment of investigations into this area. However, it is now clear that there were important caveats to these early experiments; one of which was that the nude mouse strain used was not completely immunocompromised. By the 1990s, the emergence of improved mouse models of immunodeficiency on pure genetic backgrounds allowed researchers to reassess the validity of the immunosurveillance hypothesis. The importance of endogenous interferon-γ (IFN-γ) in protecting the host from tumor development was demonstrated [9,10]. These studies showed that neutralization of IFN-γ in mice resulted in the rapid growth of tumors in the mice [9]. Furthermore, mice lacking IFN-γ responsiveness [IFN-γ receptor or signal transducer and activator of transcription 1 (STAT1, a transcription factor that is important in regulation of IFN-γ receptor signaling) were more sensitive to MCA-induced carcinogenesis compared to their wild-type counterparts [10]. Perforin, which is a cytolytic protein in cytotoxic lymphocytes, was also found to have a critical role in inhibition of tumors and in particular, B cell lymphoma development [11,12]. These key findings rekindled interest in cancer immunosurveillance. In the last two decades, remarkable advances have been made to demonstrate cancer immunosurveillance and refine

* Corresponding author at: Cancer Immunology Program, Peter MacCallum Cancer Centre, St. Andrews Place, East Melbourne, Victoria 3002, Australia.
Tel.: +61 39656 3728.
E-mail address: mark.smyth@petermac.org (M.J. Smyth).
[1] These authors contributed equally to this work.

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doi:10.1016/j.semcancer.2011.12.004

the hypothesis, with a series of publications demonstrating that mice genetically deficient in critical component of the immune system are more susceptible to spontaneous, transplantable, virus- or carcinogen-induced tumors [13–17]. The fact that the immune system has an important role in the control of tumor growth and metastasis is now a foundation of most cancer immunotherapies.

2. Cancer immunoediting

Why then do cancers occur in immunocompetent individuals despite cancer immunosurveillance mechanisms in action? Work from several groups showed that, in addition to cancer immunosurveillance, the immune system not only controls tumor quantity, but also its quality (immunogenicity) [14,15,18,19]. Tumors that develop in immunocompetent mice often grow more easily than tumors that originate from immunocompromised mice, when transplanted into syngeneic immunocompetent mice. This suggests that the immune system not only protects the host against tumor formation, but also shapes tumor immunogenicity. Immune selection pressure favors the development of less immunogenic tumors, which escape recognition by a functioning immune system. These more recent discoveries led to the formation of the concept of "cancer immunoediting", which is regarded as a refinement of the cancer immunosurveillance hypothesis [20]. We now view cancer immunoediting as a dynamic process composed of three distinct phases: elimination, equilibrium and escape.

2.1. Elimination

The elimination phase is a contemporary view of the original immunosurveillance hypothesis, in which the innate and adaptive immune systems work in concert to successfully eradicate developing tumors. Infiltration of immune cells into tumors is a well-documented observation in most, if not all, solid tumors. The tumor cell recognition mechanisms employed and how the naive immune system is activated by transformation remain quite poorly understood and our knowledge of these processes as they occur in vivo remains inferred and hypothetical. There may be many mechanisms that lead to early elimination of tumors. Stress-induced ligands, such as those recognized by the lymphocyte activation receptor, NKG2D, are one such pathway triggered by DNA damage that may alert neighboring cells to early transformation [21]. Other danger signals, that are either released by early transformed or dying tumor cells, may provide sufficient signals to alert and activate the immune system [22]. These signals may come in many different forms. In the absence of such danger signals, the immune cells may remain largely ignorant of the early transformed tissue. The elimination phase has not yet been directly visualized in vivo, largely due to an absence of investigative tools for evaluating the effects of immunity on initial tumor development.

2.2. Equilibrium

Tumor cell variants that have survived the elimination phase are proposed to enter the equilibrium phase, although the demonstration and mechanism of equilibrium remains very poorly understood. The work of Koebel et al. was an important milestone in proving the concept of an equilibrium phase [22]. Immunocompetent mice treated with a low dose of the carcinogen MCA, formed small and stable masses at the injection site for an extended time period. However, tumors rapidly appeared at the site of injection when the T cells or IFN-γ were depleted in these mice [23]. Further analysis suggested that, in contrast to the elimination and escape phases that required components of both the innate and adaptive immune systems, adaptive immunity solely maintained the equilibrium phase. Immune selection pressure, caused by the intensive interaction between immune cells and tumor cells, eventually induces the formation of tumor cells with reduced immunogenicity. These tumor cells are more capable of surviving in an immunocompetent host, which explains the apparent paradox of tumor formation in immunologically intact individuals. Immune-mediated equilibrium has recently been supported by several other important studies in mice [24,25]. As the equilibrium phase involves the continuous eradication of tumor cells and the continuous emergence of resistant tumor cell variants by immune selection pressure, it is possible that equilibrium is the longest phase of the three processes in cancer immunoediting.

2.3. Escape

After failure of most intrinsic and extrinsic tumor suppressor mechanisms, tumor cells enter the escape phase. Tumor cell escape can occur through two major changes that happen either at the tumor cell level per se and/or at the level of the tumor microenvironment. Reduction of the immunogenicity of tumor cells can lower immune recognition, such as loss of major histocompatibility complex (MHC) class I protein that presents the antigens to tumor-specific T cells or other recognition pathways (reviewed in [26]). In addition, tumor cells may acquire resistance against the cytotoxic functions of immune cells, such as expression of anti-apoptotic molecules preventing tumor cell death (reviewed in [27]). At the level of the tumor microenvironment, escape may result from the emergence of a complex immunosuppressive network within the microenvironment. Dynamic crosstalk between the tumor cells and immune cells can orchestrate this immunosuppressive network. Several factors produced by immune cells and/or tumor cells, including vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), interleukin (IL)-10, prostaglandin E_2, soluble phosphotidylserines, soluble Fas or indoleamine 2,3-dioxygenase, contribute to the establishment of an immunosuppressive microenvironment (reviewed in [28,29]). Furthermore, tumors can induce the recruitment of regulatory T cells and myeloid derived suppressor cells (MDSC), both that are regulatory immune cells capable of inhibiting host-protective anti-tumor response (reviewed in [30,31]).

3. Co-existence of cancer immunoediting and tumor-promoting inflammation

Inflammation normally functions to maintain tissue homeostasis in response to tissue stressors such as infection or tissue damage [32]. Experimental, clinical and epidemiological studies suggest a close association between inflammation and tumorigenesis. Infiltration of leukocytes into tumors was observed by Rudolf Virchow in the 19th century. He was the first to postulate a link between inflammation and cancer. Acute inflammation (i.e., innate immunity) frequently precedes the development of protective adaptive immune responses to pathogens and cancer. Enormous efforts have been made to elucidate the contribution of chronic inflammation at different stages of tumor development, including initiation, growth and metastasis. Chronic inflammation, by contrast, has been shown to contribute to tumorigenesis at all stages. It contributes to cancer initiation by generating genotoxic stress; to cancer promotion by inducing cellular proliferation; and to cancer progression by enhancing angiogenesis and tissue invasion [33]. We now appreciate that chronic inflammation orchestrates the tumor-promoting microenvironment that is intimately linked with tumorigenesis. Based on these observations, it has been proposed that inflammation and tumor immunity are mutually exclusive processes [34]. However, as discussed above, there is overwhelming evidence that anti-tumor immunity can develop to protect the host during tumor

Table 1
Role of immune cells in anti-tumor and pro-tumor immunity.

Immune cell types	Tumor-promoting	Tumor-suppressive
Macrophages	Immunosuppression (review in [149]); Promotion of angiogenesis, invasiveness and metastasis [150–152]	Production of IL-12 (reviewed in [153]) and NO [154]
Dendritic cells	Immunosuppression [155,156]; vasculogenesis [157]	Production of IL-12 and Type 1 IFN
MDSC	Suppression of anti-tumor $CD8^+$ T cells [158]; expanding regulatory T cells population [159]; induction of NK cell anergy [160]	Activation of NK cells [161]
Neutrophils	Production of cytokine [162]	Fas-ligand mediated cytotoxicity [163]
NK cells	Suppression of DC functions [164]	Production of IFN-γ; direct cytotoxicity against tumors (reviewed in [165])
NKT cells	Immunosuppression [166,167]	Production of IFN-γ [168]; direct cytotoxicity against tumors [169]
γδ T cells	Suppression of T cell immunity and dendritic cell function [170]	Production of IFN-γ [171]; direct cytotoxicity against tumors [17]
Th1 cells		Production of cytokines [172]; assist $CD8^+$ T cell immunity [173]
Th2 cells	Production of cytokine [174]	Assist in eosinophil-mediated tumor clearance [175]
Th17 cells	Production of cytokine [89]	Production of cytokine [80]; Activation of cytotoxic T lymphocytes[81]
Regulatory T cells	Immunosuppression (reviewed in [176,177])	Suppression of tumor-promoting inflammation [178]
$CD8^+$ T cells	Production of cytokine [179,180]	Production of IFN-γ [181]; direct cytotoxicity against tumors [182]
B cells	Promotion of metastasis [183,184] and tumor-favoring microenvironment [185]	Assist in $CD4^+$ and $CD8^+$ T cell immunity [186]

development. Thus, it is possible that cancer immunoediting and tumor-promoting inflammation can co-exist in the same tumor microenvironment. This notion of an overlap is supported from data generated in several mouse tumor models. Cytokines and immune cells that promote inflammation have been shown to be mandatory for MCA-induced carcinogenesis [35–37]. However, in this model we also have many examples where tumor-eliminating immunity has been demonstrated (reviewed in [38]). Similarly, in the setting of the DMBA/TPA model of skin cancers, which is known to have a large inflammatory component, some elements of the immune system, such as γδ T cells [17], IL-12 [39] and DNAM-1 [40], are integral in the immunosurveillance that prevents the formation of skin cancers. Furthermore, some cytokines have been shown not only to have pro-oncogenic effects but also to promote anti-tumor immunity. For example, TGF-β exerts its tumor-suppressive effects on tumors cells or the local microenvironment to inhibit tumor growth during pre-malignant states. However, once tumor cells circumvent the suppressive effects of TGF-β, they utilize TGF-β to their advantage to initiate tumor cell progression, invasion and metastasis (reviewed in [41]). Some tumor models might also dictate the role of cytokines during tumor development. For example, tumor necrosis factor (TNF)-deficient mice were significantly more susceptible to MCA-induced fibrosarcomas than wild-type mice, yet TNF has been reported to play a pivotal role in tumorigenesis as demonstrated in DMBA/TPA model [35,42]. Indeed TNF has both tumor promoting and anti-tumor activities in mouse and Drosophila tumor models [43], and more recent work has shown that in a mouse melanoma model, IFN-γ is required both for ultraviolet B (UVB)-induced tumor formation and for immune rejection of these tumors [44]. It becomes increasingly evident that many immune cell types are potentially bi-functional during tumor development and may display both tumor-promoting and tumor-suppressive capabilities (Table 1). Therefore, further study of the distinctions between the pro-tumor and anti-tumor activities of some immune cells is warranted in order to develop more effective immunotherapies.

4. Tumor-associated inflammation versus therapy-induced inflammation

It is now well established that inflammation has paradoxical roles during tumor development. The net outcome of tumor-associated inflammation depends on the dominance of either tumor-promoting or tumor-suppressive actions. Recently, emerging evidence showed that cancer therapy may induce a strong inflammatory response [45–47] (Fig. 1). Radiotherapy and some chemotherapies result in substantial tumor cell death, which in turn triggers a local and/or systemic inflammatory response capable of enhancing the cross-presentation of tumor-associated antigens. Through this work, we now recognize that some cytokines play seemingly opposing roles in tumor-associated inflammation and therapy-induced inflammation.

4.1. High mobility group B1 (HMGB1)

Damage-associated molecular pattern (DAMP) molecules, including HMGB1, are danger signals that can initiate and propagate immunity in response to infectious insults or tissue injury. HMGB1 functions as a nuclear non-histone protein and plays a role in the facilitation of both protein–protein interaction and gene transcription (reviewed in [48]). HMGB1 can be passively released from necrotic cells or actively secreted by immune cells into the local microenvironment. Extracellular HMGB1 can function to promote inflammation by numerous mechanisms, including stimulating neutrophils or monocytes to produce and secrete pro-inflammatory cytokines and chemokines [49,50]. Furthermore, HMGB1 is able to activate endothelial cells, promoting angiogenesis and migration of immune and stem cells, thereby initiating an inflammatory response [51–53]. HMGB1 also induces the maturation of DCs including the up-regulation of co-stimulatory molecules [54,55]. HMGB1 can bind to the receptor for advanced glycation end products (RAGE), and Toll-like receptors (TLR2 & 4) to trigger the inflammatory pathway [56,57]. HMGB1/DNA complexes can also bind TLR9 to promote inflammation [58] [59]. Several studies have shown that HMGB1 is involved in the development of tumors [60–62]. Elevated expression levels have been found in several types of tumors, such as melanoma [63], prostate [64], colon [65], pancreatic [66], and breast cancer [67]. The inhibition of apoptosis of tumor cells as a consequence of over-expression of HMGB1 suggests that this molecule might also act as an anti-apoptotic protein [65]. In addition, HMGB1 has been described to act as a pro-angiogenic oncoprotein during tumor development [52,53]. Furthermore, HMGB1 secreted by dying tumor cells during chemo- or radiotherapy triggers the activation of IFN-γ polarizing tumor-antigen specific T-cells [45]. This therapy-induced inflammation is TLR4- and MyD88 dependent. HMGB1 released from the dying tumor cells is also indispensable for efficient processing and cross-presentation of tumor antigens.

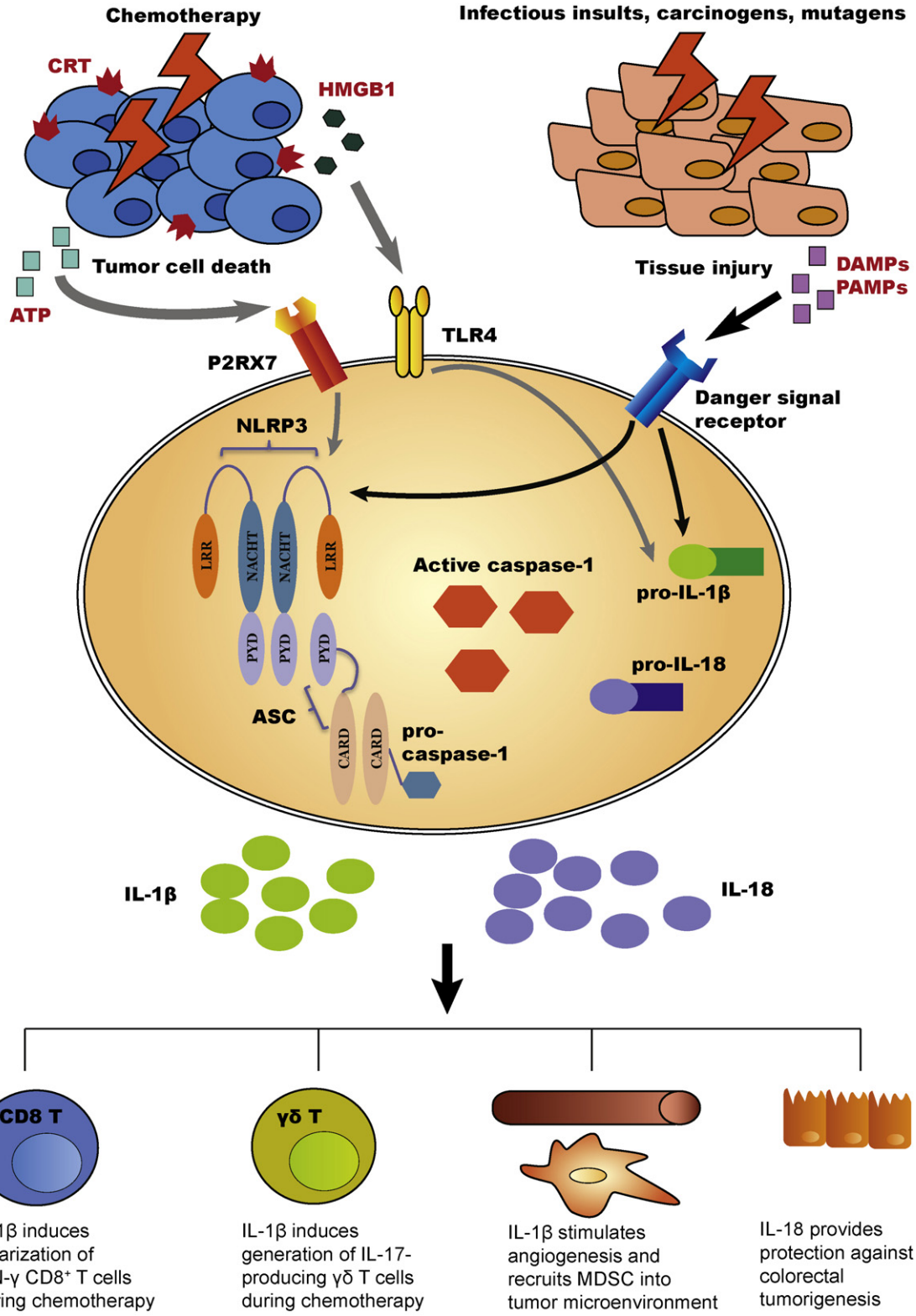

Fig. 1. Role of danger signal receptor signaling pathway in tumor development and chemotherapy. Danger signals that released as a result of chemotherapy or tissue injury may be recognized by the danger signal receptors, such as TLRs and P2RX7 receptor. In turn, this can trigger the downstream inflammatory responses that might be beneficial or detrimental to the host. During chemotherapy, crosstalk between tumor cells and DCs that involves ATP/P2RX7 and HMGB1/TLR4 molecular interactions triggers the inflammasome/IL-1β-associated signaling pathway, which is important for the anti-tumor response. In the context of tissue injury caused by infectious insults, carcinogens or mutagens, DAMPs or PAMPs bind to the danger signal receptor and stimulate the inflammasome/IL-1β/IL-18-associated signaling pathway. IL-1β and IL-18 secreted from the cells can then exert various effects in the host and mediate different immune responses depending on the context of inflammatory microenvironment.

4.2. Adenosine triphosphate (ATP)

ATP has an important pro-inflammatory action as a danger signal. ATP is actively released in the extracellular environment in response to tissue damage and cellular stress. Through the activation of P2X and P2Y receptors, extracellular ATP enhances tissue repair, promotes the recruitment of immune phagocytes and DC, and acts as a co-activator of NLR family, pyrin domain-containing 3 (NLRP3) inflammasome. Dying tumor cells emit danger signals that are perceived by DC, which link innate and cognate immune responses. Recently, we observed that ATP was released by tumor cells dying in response to chemotherapy. ATP activates purinergic P2RX7 receptors on DC, thus activating the NLRP3/ASC/caspase-1 inflammasome and driving the secretion of IL-1β. IL-1β then is required for the adequate polarization of IFN-γ-producing $CD8^+$ T cells (reviewed in [68]). These results imply a novel danger signal, ATP, and a novel receptor, P2RX7, in the chemotherapy-elicited anticancer immune response. Importantly, we showed that a loss-of-function allele of P2RX7 that reduces the affinity of P2RX7 receptor for ATP compromises the efficacy of anthracycline-based chemotherapy in breast cancer patients, implying that the pathway we elucidated has clinical relevance (reviewed in [68]).

Adenosine accumulates in inflammation but it is more than an end-product of ATP catabolism. Signaling through different receptors with distinct, cell-specific cytoplasmic pathways, adenosine is now recognized as an inducible switch that regulates the immune system [69]. By acting through the A(2A)AR, adenosine shapes T cell function, largely by conferring an anti-inflammatory tone on effector Th cells (Teffs) and natural killer (NK) T cells. In contrast, both the A(2A)AR and A(2B)AR are expressed by APC which have been shown to regulate innate responses and the transition to adaptive immunity. In particular, the conversion of extracellular ATP to adenosine essentially through the enzymatic activity of the ecto-nucleotidases CD39 and CD73, acts as a negative-feedback mechanism to prevent excessive immune responses. Coupled with this work, there is also emerging evidence that adenosine production is one mechanism that allows some neoplasms to evade host defenses [70,71].

4.3. Calreticulin (CRT)

CRT from vertebrates is a calcium-binding protein present mainly in the endoplasmic reticulum (ER). There, it directs the conformation of proteins and controls calcium levels. The phagocytic uptake of apoptotic/necrotic cells involves a plethora of molecules, including immunoglobulins, lectins, components of the complement system (all of which act as opsonins), as well as the phospholipid phosphatidylserine and CRT, both of which can be exposed on the surface of dying cells. For a long time, surface-exposed CRT was believed to participate in phagocytosis, mostly as a co-receptor for specific opsonins. But recent evidence suggests that the pre-apoptotic surface-exposure of calreticulin may dictate the immune response to tumor cells that succumb to anti-cancer treatments [72].

4.4. IL-17A

IL-17A is secreted by activated $CD4^+$ T cells (termed Th17 cells), NKT cells and γδ T cells [73–77]. IL-17A has pro-inflammatory properties that induce the expression of granulocyte colony stimulating factors, chemokines and pro-inflammatory cytokines, such as TNF, IL-1β and IL-6. Notably, IL-17A plays a key role in the recruitment and activation of neutrophils. IL-17 is also essential for the host protection against extracellular pathogens. However, in some circumstances, IL-17-driven inflammation is no longer protective, but carries the risk of severe immunopathology (reviewed in [78,79]). Although extensive studies have been performed to elucidate the role of IL-17 in tumor development, its role still remains controversial. Th17 cells were found to be more effective than Th1 cells in eliminating established tumors [80]. In addition, IL-17 can inhibit tumor growth by increasing the generation and activity of cytotoxic T lymphocytes [81]. IL-17-deficient mice were reported to display increased numbers of lung metastases and rapid tumor growth of MC38 colon adenocarcinoma compared with wild-type controls [82]. In the setting of therapy-induced inflammation, IL-17A signaling was demonstrated to be required for the generation of IFN-γ-secreting tumor antigen specific-T cell immunity during chemotherapy [47,83]. The effectiveness of mounting this protective anti-tumor immunity depends on IL-17 production, mainly from γδ T cells. Furthermore, these studies showed that IL-23, which is an important inducer of IL-17 production, is dispensable in this specific therapeutic response. By contrast, IL-17A is able to induce a wide range of angiogenic mediators, including VEGF and IL-8 [84–86]. Furthermore, IL-17A might also induce IL-6 production to promote tumor growth [87]. We and others have shown that IL-17A is critical for DMBA/TPA-induced skin tumors and colon tumors [36,88,89]. However, in many tumor models, we reported that tumor growth and metastases development was comparable in both IL-17A-deficient and wild-type mice [36,90].

4.5. IL-1β

IL-1β is a key pleiotropic pro-inflammatory cytokine produced by antigen presenting cells and known to mediate acute immune responses, providing a link between the innate and adaptive immune responses. In the context of immunogenic chemotherapy, IL-1β is required for the adequate polarization of IFN-γ-producing $CD8^+$ T cells. In the absence of the IL-1 receptor 1 (IL-1R1) or in the presence of IL-1 receptor antagonist, dying tumor cells fail to prime cancer specific IFN-γ producing $CD8^+$ T cells [46]. Furthermore, IL-1β plays a crucial role in stimulating IL-17 production and the generation of anti-tumor γδ T cells [47,83]. γδ T cells that were deficient in IL-1R1 lost their ability to amplify the action of anthracycline chemotherapies. Excessive IL-1β production has been implicated in chronic inflammatory diseases and malignancies (reviewed in [91,92]). Several studies support the finding that production of IL-1β pro-inflammatory cytokines in the pathogenesis of DMBA/TPA-initiated skin cancers, MCA-induced fibrosarcomas and B16 melanoma tumors (Fig. 1) [35,37,93]. However, the role of IL-1β in tumor metastases still remains debated [93,94]. IL-1β can induce the recruitment of myeloid-derived suppressor cells to the tumor site to suppress the anti-tumor response [95] [96]. Furthermore, IL-1β can promote angiogenesis to facilitate the tumor growth [93,97].

It would seem that both IL-1β and IL-17 act to either promote tumor initiation or suppress tumor growth in the context of inflammation caused by therapeutic intervention. This paradox might be explained by the type of cell making the cytokine, the stimuli that cell is receiving, and its relationship to the tumor itself. These complexities are yet to be unraveled.

5. Danger signals, inflammation and cancer immunoediting

The innate immune system is the first line of host defense against infectious insults and tissue injury. Unlike the adaptive response, which is based on an expansive repertoire of antigen-specific antibodies and T cells with various T cell receptors, innate immunity relies on the recognition of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs)(Fig. 1). The key component of the innate immune system is the pattern recognition receptor (PRR), such as TLR and NOD-like

receptor (NLR), which is responsible for the recognition of PAMPs and/or DAMPs and generation of the subsequent immune response. Various levels of crosstalk between TLR and NLR pathways have been demonstrated to be critical in initiating the inflammatory response. However, defective functions of TLR or NLR might lead to disturbed inflammatory responses, causing morbidity and mortality.

5.1. Toll-like receptors

TLRs are a family of transmembrane proteins with a leucine-rich repeat extracellular domain and with a cytoplasmic tail largely composed of the Toll interleukin-1 receptor domain [98]. Human and mouse TLRs consist of a large family with at least 13 members (reviewed in [99]). Studies using gene-targeted mice have identified a diverse array of exogenous and endogenous ligands for the TLRs. The best-characterized TLR microbial ligands are as follows: bacterial lipoproteins, lipotechoic acid and zymosan, which activate TLR1, TLR2 and TLR6; lipopolysaccharide, which stimulates TLR4; flagellin, which stimulates TLR5; profilin, which activates TLR11; demethylated CpG motifs, double-stranded RNA and single-stranded RNA act as stimulators of TLR9, TLR3 and TLR7/8 respectively. Extensive work in the past decade has suggested an increasing number of endogenous products may serve as potent activators of the TLRs, particularly TLR2, TLR3 and TLR4. These include heat shock proteins [100,101], HMGB1 [57], uric acid crystals [102], fibronectin [103], hyaluronan [104,105] and messenger RNA [106]. Following ligand binding to TLRs, TLRs dimerize and transmit through either a myeloid differentiation factor 88 (MyD88)-dependent pathway or -independent pathway that is only selective to TLR3 and TLR4. Activation of TLRs lead to recruitment of one or more of four adaptor proteins, including MyD88, MyD88 adaptor-like (Mal), TIR-domain-containing adaptor-inducing interferon-beta (TRIF) and TRIF-related adaptor molecule (TRAM), subsequently initiating their specific signaling cascade that involves NF-κB, mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K) and/or interferon regulatory factor (IRF) (reviewed in [107]). This enables a tailoring of the immune responses to specific ligands. Although TLRs are well known for their role in host defense against microbial infection, other functions attributed to TLR signaling include various aspects of host homeostasis, such as apoptosis, tissue repair and regeneration [108,109]. Furthermore, TLRs have an important role in regulation of T cell- and B cell-mediated immune responses (reviewed in [110,111]).

TLRs are potent activators of the NF-κB pathway which is known to link chronic inflammation and tumor development. Therefore, TLRs likely mediate some of the effects of the immune system in tumor development. However, the role of TLRs in cancer is far from completely understood. Current evidence suggests that TLRs play a dual role in cancer development. The importance of TLRs in tumor immunity is demonstrated by an increasing body of evidence that shows that genetic polymorphisms in the TLRs are associated with cancer risk (reviewed in [112]). TLR4-variants are associated with increased risk of developing prostate cancer and *Helicobacter pylori*-induced gastric cancer [113–115]. Single nucleotide polymorphisms in TLR1, TLR6 and TLR10 were also reported to alter the susceptibility to prostate cancer [116]. TLR4- and TLR10-sequence variants are associated with nasopharyngeal carcinoma risk [117,118].

A number of recent studies have investigated tumor development in mice that lack TLRs or TLR adaptor proteins. MyD88 was shown to be crucial for the promotion of diethylnitrosamine-induced hepatocellular carcinoma, spontaneous and carcinogen-induced intestinal tumorigenesis, DMBA/TPA-induced papilloma and MCA-induced fibrosarcoma [35,119,120]. However, MyD88 is an adaptor protein not only used by TLRs, but also by IL-1R1 and IL-18R. Thus, any such results using MyD88-deficient mice cannot directly attribute a role of TLR in tumor development, since we cannot exclude the possible contribution of IL-1R1 and IL-18R pathways in tumorigenesis. TLR4-deficient mice were protected against colitis-associated neoplasia, where TLR4 was responsible for the induction of cyclooxygenase-2 and prostaglandin-E_2 production and regulation of epidermal growth factor receptor signaling pathway [121,122]. In addition to its action in the intestinal tract, TLR4 was also reported to be involved in two-step chemically-induced skin carcinogenesis [123]. A recent study documented that versican, a tumor derived factor, can activate tumor-infiltrating myeloid cells through TLR2 and its co-receptors TLR6 and CD14 and elicit the production of pro-inflammatory cytokines [124]. Furthermore, another study showed that blocking TLR2 activity markedly reduced B16 pulmonary metastases by reversing the tumor-induced immunosuppressive microenvironment and restoring the anti-tumor immunity [125]. Although most of the studies showed the tumor-promoting function of TLRs, one study by Chin et al. demonstrated that suppression of TRAMP prostate cancer is mediated by TLR3 [126]. However, the tumor suppressive mechanism of TLR3 was not characterized by the authors and requires further elucidation.

TLRs are not only expressed on immune cells, but also on tumor cells. A recent study demonstrated that activation of TLR4 on tumor cells by LPS caused tumor immunoevasion [127] [128]. Furthermore, inhibition of TLR3 in head and neck squamous cell carcinoma resulted in decreased cell proliferation [129]. However, TLRs that are expressed on tumor cells might also be detrimental for the tumor itself. Two independent studies showed that direct stimulation of TLR3 on tumor cells can induced the apoptosis of tumor cells [130,131]. Furthermore, Cai et al. showed that activation of TLR5 on breast cancer cells can inhibit cell proliferation and tumor growth [132]. Together, these data suggest that activation of TLRs on tumor cells can be either beneficial or detrimental for the host. By contrast, emerging evidence showed that TLRs play a role in the efficacy of chemotherapy or radiotherapy. A recent study suggested that TLR4 and MyD88 play a critical role in anti-tumor response following chemotherapy or radiotherapy [45]. After treatment with doxorubicin, oxaliplatin or radiotherapy, tumor growth was suppressed in wild-type mice, but not in TLR4-deficient mice.

5.2. Inflammasomes

The discovery of TLRs provided a class of sentinel receptors that detect pathogenic microbes and trigger anti-pathogen signaling cascades. Recently, intracellular microbial sensors have been identified, including NLRs (reviewed in [133,134]). Some of the NLRs also sense non-microbial danger signals and form large cytoplasmic complexes called the inflammasome (reviewed in [135,136]). In response to danger signals, the NLR, such as NLRP3, interacts with the adaptor molecule apoptosis-associated speck like protein (ASC) to form the inflammasome, the principal caspase-1 activation complex (Fig. 1). The inflammasome functions as a platform that stimulates caspase-1 activation to mediate the maturation and secretion of pro-inflammatory cytokines-IL-1β and IL-18. Mutated inflammasomes may cause more production and secretion of IL-1β that has a detrimental role in various diseases including autoinflammatory diseases, such as gout. The NLRP3 inflammasome currently is the best-characterized. Among hematopoietic cells, NLRP3 expression was almost exclusively found in cells expressing the myeloid marker CD11b, including neutrophil, macrophage, monocytes and conventional dendritic cells [137]. The inhalation of airborne pollutants, such as asbestos or silica, is linked to inflammation of the lung, fibrosis and lung cancer (reviewed in [138–140]). Silica and asbestos dust which

can activate the NLRP3 inflammasome are strong inflammation inducers in the lungs [141]. As the dust becomes lodged in the lungs, chronic inflammation develops in the host, resulting in an environment that favors the development of cancer. This, in particular with asbestos, is associated with the development of malignant mesotheliomas. It is significant to note that after in vivo inhalation of asbestos or silica, pulmonary inflammation is greatly decreased in NLRP3-deficient mice [141]. However, it is still not clear if NLRP3 inflammasome plays a critical role in development of asbestos-associated malignant diseases.

Ulcerative colitis (UC) is a risk factor for developing colorectal cancer and is a good example of the link between inflammation and cancer in the gastrointestinal tract. Several molecular players, including the TLRs, have emerged as mediators of UC and colorectal cancer. The NLRP3 inflammasome functions as a negative regulator of tumorigenesis during experimental colitis [142]. To determine the effects of the NLRP3 inflammasome on ulcerative colitis, a mouse model that uses dextran sulfate sodium (DSS) to induce UC was utilized. Unexpectedly, when compared with wild-type mice, caspase1$^{-/-}$, ASC$^{-/-}$ or NLRP3$^{-/-}$ mice were highly susceptible to DSS-induced colitis. Moreover, knock out of the NLRP3 inflammasome components led to loss of epithelial integrity, resulting in systemic dispersion of commensal bacteria, massive leukocyte infiltration, and increased chemokine production in the colon during experimental colitis. Work from two more independent research groups supported these results [143,144]. However, using the same model, Bauer et al. showed that NLRP3$^{-/-}$ mice were less susceptible to the development of UC [145]. Interestingly, IL-18 has been shown to provide protection from colorectal tumorigenesis [146]. But a more recent study demonstrated that inflammation-induced tumorigenesis in the colon was regulated by the NLRC4 inflammasome, rather than the NLRP3 inflammasome [147]. Given the opposing results obtained from different groups, the role and mechanism of the NLRP3 inflammasome in the development of UC and colorectal cancer awaits further elucidation.

Standard first line therapies, such as chemotherapy and radiation, were not thought to provoke natural immunity to cancer, but recent findings demonstrating that dying tumor cells present and release key signals to stimulate or evade neighboring leukocytes are challenging that view. The therapeutic efficacy of anticancer chemotherapies may depend on the capacity of DC to present antigen from dying cancer cells and to prime tumor-specific IFN-γ-producing CTL [46]. Dying tumor cells release ATP, which then acts on P2RX7 purinergic receptors from DC and triggers the NLRP3 inflammasome allowing for the secretion of IL-1β (Fig. 1). In the absence of the IL-1 receptor 1 or in the presence of IL-1 receptor antagonist, dying tumor cells failed to prime cancer-specific, IFN-γ-producing CD8$^+$ T cells. Moreover, T cell priming by dying tumor cells failed in NLRP3$^{-/-}$ or caspase-1$^{-/-}$ mice. Accordingly, anticancer chemotherapy that was successful in immunocompetent hosts was inefficient against tumors established in P2RX7$^{-/-}$ or NLRP3$^{-/-}$ or caspase-1$^{-/-}$ hosts and WT mice neutralized for IL-1β, but not IL-1α. Furthermore, breast cancer patients treated with anthracyclines and carrying a loss-of-function allele of *p2rx*$_7$ develop metastatic diseases more rapidly than patients bearing the normal *p2rx*$_7$ allele. These results indicated that the NLRP3 inflammasome links the innate and adaptive immune systems and controls adaptive immune responses against dying tumor cells.

A recent study found that the NLRP3 deficiency in the host resulted in a four-fold increase in tumor responsiveness to a therapeutic cancer vaccine [148]. This finding suggested an unexpected role for NLRP3 in cancer vaccines and may provide a potential pharmacologic target to increase vaccine efficacy. At first glance, the detrimental role of the NLRP3 inflammasome in such a vaccine setting is surprising, as one might expect that the pro-inflammatory cytokines produced would create favorable conditions for the generation of an adaptive response. The study discovered that deleting the NLRP3 proteins reduced the infiltration of tumor-associated MDSC to the tumor site and thus then enhanced the generation of anti-tumor response. This finding was the first to link the interaction between NLRP3 and MDSC to cancer vaccines.

6. Conclusions and perspectives

The influence of inflammation on tumorigenesis, and even on cancer therapy, is evidently significant. However, as mentioned above, many of the inflammatory mediators can benefit the host in therapy of tumors despite also having a critical role in cancer development and progression. The dual role of certain molecules is far from being completely understood. Currently, the markers that we use for immune cell phenotyping might not be very useful in functionally differentiating these immune cells in a tumor microenvironment. Given that DAMPs are emerging as critical modulators of the inflammatory response, more attention is needed to demonstrate the role of DAMPs-associated receptors and their signaling pathways in tumor development. Some inflammatory cytokines have been shown to be required for the efficacy of cancer therapy, but many inflammatory mediators can abrogate the effect of therapeutics, even promoting tumor resistance to the therapy. Clearly, a better insight into tumor-associated inflammation will help us to develop the effective cancer therapy or even prevention.

Conflict of interest

The authors declare they have no conflict of interest.

Funding

NH&MRC of Australia.
Victoria Cancer Agency.
Association for International Cancer Research.
Cancer Research Institute.
These funding bodies do not have any part in this manuscripts content.

Acknowledgements

The authors thank Lionel Apetoh for helpful discussions. This work was supported by the National Health and Medical Research Council of Australia (NH&MRC) Program Grant (454569), the Victorian Cancer Agency, and the Association for International Cancer Research (AICR). AM was supported by a NBCF Research Fellowship. MJS received support from a NH&MRC Australia Fellowship. MTC was supported by a Cancer Research Institute PhD scholarship.

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