



NLRP3 Inflammasome Enhances Tumor Growth

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Abstract

Tumor cell derived danger signals known as DAMPs activate the NLRP3 inflammasome leading to IL-1 β /IL-18 production conferring a pro-inflammatory environment. The inflammatory tumor environment enhances the tumor progression and metastasis. The NLRP3 inflammasome or IL-1/IL-18 represents promising therapeutic targets in cancer therapy, which is discussed in this review. Alternative targets such TLRs and cGAS/STING dependent immune regulators need to be considered. The metabolome and microbiome of the host are additional factors contributing to a successful chemo- and immunotherapy.

Inflammation Driving Tumor Growth

Tumors are commonly infiltrated by inflammatory and immune cells which affect the local and metastatic growth. While immune cells infiltrating the tumor may control tumor cell growth, inflammatory cells in tumor microenvironment may enhance and spread of tumor cells, which is well documented [1]. In fact, chronic systemic or local inflammation with the release of pro-inflammatory cytokines and chemokines activates several fundamental pathways such as TLR [2], NLR [3], and nucleotide sensor [4-6], which drive inflammation. Here, the focus is on NLRP3 inflammasome, but a role of TLR and cGAS-STING pathways is briefly discussed.

Inflammation Role of NLRP3 Activation with IL-1 Release

The NLRP3 inflammasome is a major regulator of Interleukin-1 β (IL-1 β) and IL-18 production [7]. NLRP3 inflammasome is a multimeric cytosolic protein complex formed in response to cellular stress and metabolic perturbations, which activates caspase-1, with release of the inflammatory cytokines IL-1 β and IL-18 and inflammatory cell death (pyroptosis). Aberrant NLRP3 activation drives chronic inflammatory diseases and regulates cancer progression. The inflammasome is activated by cell stress and several danger signals such as DNA, nucleotides, ATP, proteases, particles and others [8-11]. Activated NLRP3 recruits the adaptor protein ASC forming a polymer complex activating caspase 1 enabling the maturation of IL-1 β and IL-18 [11], which are highly inflammatory cytokines (Figure 1).

NLRP3 activation drives cell proliferation and metastasis [12]. IL-1 β released by Inflammasome activation is a major regulator of inflammation, immunity and tumor response [13]. Tumor Necrosis Factor (TNF α) is another mediator of inflammation involved in cancer development [14,15]. NLRP3 inflammasome-mediated inflammatory cytokines play either a detrimental in the pathogenesis of inflammatory and metabolic diseases or may have beneficial effects in infectious diseases and some cancers, which need to be considered for therapeutic targeting this pathway [7].

Inflammasome and IL-1 Inhibition

In view of the pro-inflammatory effect of the NLRP3 inflammasome, which is often activated in cancer, enhances tumor growth. The therapeutic targeting of NLRP3 is of major interest [16]. Inhibitors of the NLRP3 inflammasome are in development in several laboratories. MCC950 is a selective, small-molecule inhibitor blocking NLRP3 activation, but not the AIM2, NLRC4 or NLRP1 inflammasomes (not discussed here) as reported [17]. MCC950 blocks the formation of the inflammasome complex and thereby inhibits IL-1 β production *in vitro* and *in vivo*. MCC950 attenuated Experimental Autoimmune Encephalomyelitis (EAE), modeling multiple sclerosis in patients. MCC950 is a great tool to study the role of inflammasome in human health and disease [17,18]. Other NLRP3 inhibitors are in preclinical development [19]. Data in human patients are as yet scarce. The efficacy of MCC950 in the treatment of murine ulcerative colitis suggests it as a potential novel therapeutic to treat human inflammatory bowel diseases and colon cancer [20] and rare autoimmune diseases [21]. MCC950 analogues and other NLRP3 inhibitors are in development

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and are under evaluation. Furthermore, a small-molecule P2RX7 agonist activated inflammasome and promoted antitumor immune responses and sensitize lung tumor to immunotherapy with improved survival of mice. Mechanistically, activation of P2RX7 lead to increased NLRP3-dependent production of IL-18 activating NK and CD4+ T cells to produce IFN- γ increase tumor immunogenicity. Activation of P2RX7 combined with α PD-1 immune checkpoint inhibitor allowed tumor regression, followed by a robust immunological memory response [22].

Based on the fact that IL-1 β driving inflammation and tumor growth [15,23,24], it is expected that blocking the natural IL-1 receptor antagonist, IL-1ra/Anakinra, or neutralizing IL-1 β antibodies likely have a place in tumor therapy [25].

A recent report demonstrates that Metformin, used to treat diabetes and cancer, inhibits macrophage ATP dependent mitochondrial DNA synthesis and thereby blunts NLRP3 activation revealing a new mechanism of action for Metformin to inhibit inflammation, which may also explain its beneficial effect in tumor therapy [26]. Several other inflammasome inhibitors will emerge in view of the novel targetable pathway in oncology.

Therefore, the inhibition of the inflammasome and IL-1R activation represent important therapeutic approaches to follow in the future.

Cancer Chemotherapy and NLRP3 Activation

Chemotherapy and radiotherapy are the first therapeutic choice to kill tumor cells and reduce tumor growth, which are not reviewed here. However, recent studies revealed that the chemotherapeutic agents' gemcitabine and 5-fluorouracil unexpectedly activated the inflammasome, promoting tumor growth [27]. NLRP3 activated in Myeloid-Derived Suppressor Cells (MDSCs) triggering IL-1 β secretion via lysosomal release of cathepsin- B activating caspase-1. MDSC-derived IL-1 β induced secretion of Th17 cells, which blunts

the anticancer efficacy of the chemotherapy. Therefore, activation of the NLRP3 inflammasome in MDSCs may limit the antitumor efficacy of chemotherapeutic agents.

Neutrophils play a role as recently demonstrate that the phosphatase oncoprotein PPM1D/Wip1 is a negative regulator of p53 and its over expression in several human solid tumors is associated with poor prognosis. Mice deficient for Ppm1d have abundant neutrophils and reduced growth of syngeneic murine melanoma or lung carcinoma. Chemical inhibition of Wip1 in human or mouse neutrophils enhances the anti-tumor effect, p53-dependent expression of co-stimulatory ligands and proliferation of co-cultured cytotoxic T cells. Thus, inhibition of Wip1 in neutrophils enhances immune anti-tumor responses and represents a new therapeutic target [28]. Further, accumulation of β 2 m in macrophages associated with human multiple myeloma leads β -fibrils formation lysosomal rupture, inflammasome activation and IL-1 β and IL-18 secretion. Inhibition of NLRP3 with MCC950 reduces multiple myeloma in the murine model [29].

Beyond myeloid cells, T cells and adaptive immunity are critical to prevent tumor progression. We showed that NLRP3 is transcription factor driving a protective Th2 response [30]. Importantly, T cell differentiation into the different subsets of T cells, such as Th1, Th2, Th9, and Th17 depends on the cytokine tumor environment, chemotherapy and tumor cell properties [31,32]. In addition to myeloid cells, neutrophils and T cells, innate lymphocyte emerged to contribute to the tumor immune response [33].

Furthermore, tumor antigen-specific T-cell immunity that involves the danger signals High-Mobility-Group Box 1 (HMGB1), an alarmin protein secreted by dying tumor cells activating the Toll-like receptor 4. During chemotherapy or radiotherapy, dendritic cells require signaling through TLR4/MyD88 for efficient processing and cross-presentation of antigens from dying tumor cells. Importantly, the therapeutic effect of chemotherapy is reduced in TLR4 and

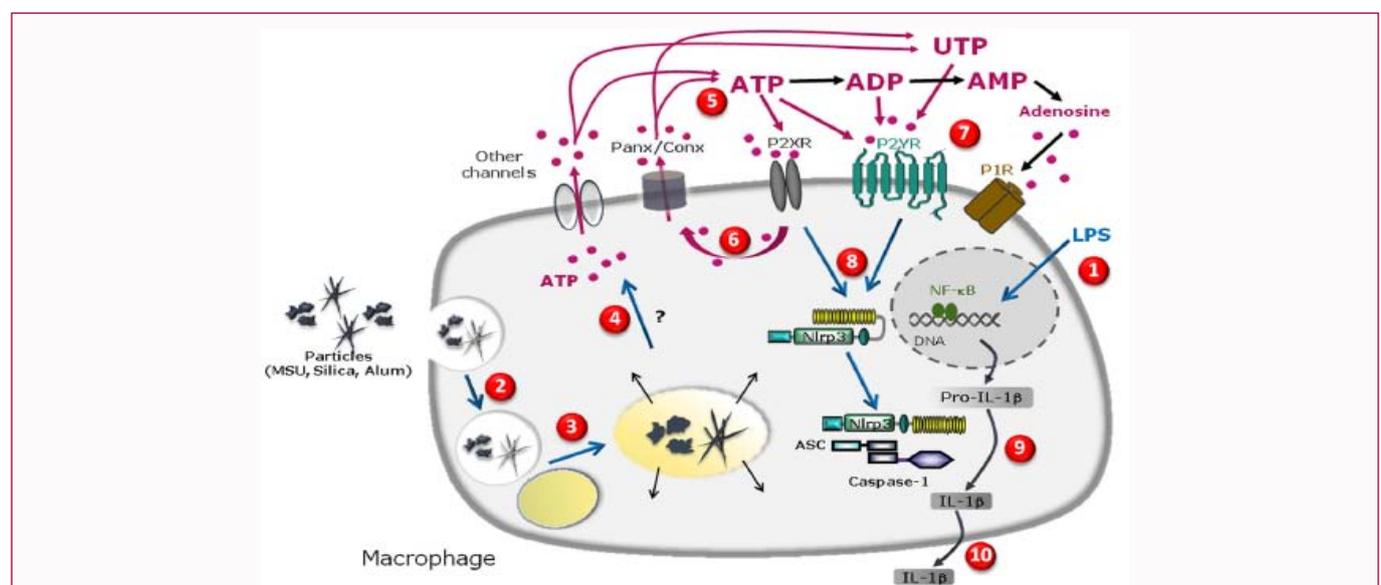


Figure 1: Schematic diagram illustrating the specific cascade and signaling pathway in LPS-primed macrophages stimulated with MSU, silica or alum salt crystals. LPS priming induces transcription of pro-IL-1 β gene and other genes in the nucleus upon activation of the transcription factor NF κ B and subsequent production of pro-IL-1 β protein in the cytosol (1). Particle internalization (2), fusion to lysosome (3) and further phagolysosome destabilization may lead to cathepsin leakage (4) which precedes pannexin/connexin (Panx/Conx) hemichannel and purinergic signaling-dependent intracellular ATP release (5). Extracellular ATP may act through P2X7 receptor to amplify ATP release in a P2X7 receptor-dependent way (6). ATP, UTP or their derived degradation products such as ADP, UDP, and adenosine, generated by ecto-endonucleases, may act through an autocrine loop on other purinergic receptor P2X, P2Y, and/or P1 receptor (7) leading to NLR3 receptor activation (8). This allows inflammasome complex formation and maturation of pro-IL-1 β to IL-1 β production (9) and IL-1 β secretion (10).

MyD88 deficient mice, and breast cancer patients carrying a TLR4 loss-of-function allele. Thus, the results delineate a clinically relevant immune-adjutant pathway triggered by tumor cell death is mediated by TLR-4 [34].

Microbiome and Cancer

The microbiota plays an important role in the host immune response. Tumor growth and intense tumor therapy may cause changes in the composition of the intestinal microbiota known as dysbiosis [35,36], which is involved in the immune response, but also affects the composition of the tumor environment and the response to therapy. The anti-cancer effect of cyclophosphamide is profoundly modulated by the microbiota and the therapeutic effect [37]. Furthermore, gut microbiota enhanced the effect of PD-1 based immunotherapy of epithelial tumors in patients. The transfer of fecal microbiota transplantation or transfer of *A. mucinophila* restored the efficacy of PD-1 blockade in mouse tumors [38]. The role of the microbiome in human cancer is a field of intense research [39].

Other Pathways -Toll-Like Receptor (TLR) and cGAS-STING Activation as Therapeutic Targets

We showed that DNA and other DAMPS activate the TLR pathway leading IL-1/NFκB activation and inflammation [8,40]. Recently, DNA sensing cGAS-STING pathway leading to type I interferon dependent inflammation and T cell activation was discovered as an important pathway of inflammation [41-43]. Recent developments revealed that both the TLR and the cGAS-STING are therapeutic targets [15], which need to be explored further.

In conclusion, Tumor derived DAMPS activate the NLRP3 inflammasome leading to IL-1/IL-18 secretion rendering a pro-inflammatory environment, which alters tumor progression and enhances metastasis. Inflammasome NLRP3 or IL-1/IL-18 inhibition of inflammation identifies promising therapeutic approaches in cancer therapy. However, additional targets such TLRs and cGAS/STING dependent immune regulators, the microbiome and metabolome of the host are factors to be considered for a successful chemo- and immunotherapy.

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