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Mini-review

Inflammasomes as molecular mediators of inflammation and cancer: Potential role in melanoma

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ABSTRACT

The inflammasome is a multi-protein complex that mediates immune responses to microbial, host, and environmental signals. When active, inflammasomes regulate caspase-1 activation and IL-1β secretion. There is a strong link between inflammation and cancer, and IL-1β is one of the major molecules involved in both of these disease processes. Here we review the role of inflammasomes in regulating IL-1β secretion, and the impact of this pathway on cancer pathogenesis, with a focus on melanoma. This represents an exciting new area of research, and could potentially result in new targets for melanoma therapeutics in the future.

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1. Introduction

The link between cancer and inflammation is well known [1]. Inflammation was initially believed to be a host response against tumors, leading to tumor suppression and favorable prognosis [2]; however, evidence increasingly suggests that inflammation can also be associated with unfavorable clinical prognosis in cancer patients [3,4]. In human and mouse models, tumor cells secrete pro-inflammatory cytokines such as TNF and IL-1, chemokines including CXCL8 (also known as IL-8), and other soluble factors which promote tumor development and progression [1,5,6]. While cytokines are known to have an important role in cancer pathogenesis, many cytokines have both tumor-inhibitory and tumor-promoting activities [7,8]. It has become increasingly evident however, that IL-1β is one of the critical pro-inflammatory cytokines involved in tumor pathogenesis [9–14], and inflammasomes play a significant role in the pathway regulating IL-1β secretion [15–19]. Moreover, constitutional activation of this pathway was recently observed in human melanoma cells [20], which could represent a novel target for future melanoma therapeutics. Here, we present our current understanding of the biology of IL-1β, its regulation by inflammasomes, and the role of this pathway in tumor biology, specifically in melanoma.

2. Melanoma and inflammation

2.1. Melanoma

Melanoma, the most aggressive form of skin cancer, results in 8790 deaths per year in the US [21]. In contrast with many other cancers, the incidence of melanoma is increasing [21,22] and the treatment for metastatic melanoma continues to be challenging. Investigating the biological mechanisms underlying melanoma progression

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and drug resistance is thus critical for developing effective therapeutic intervention against advanced melanoma.

Recent studies on gene polymorphisms in melanoma, especially single nucleotide polymorphisms (SNPs), have demonstrated that genotypes of cytokines such as IL-6, TNF-α, IFN-γ, IL-10 and TGF-β1 may play a role in melanoma progression and escape from immunosurveillance [23]. In addition, IL-1β-511 TT genotype was demonstrated to be associated with thinner invasive melanomas at presentation [24].

Human melanoma cells produce a number of cytokines that are known to be associated with invasiveness and aggressiveness [25]. These include IL-6, IL-8, CXCL1–3 (MGSA-GROα-γ), CCL5 (RANTES) and monocyte chemotactic protein-1 (MCP-1, also known as CCL2). All of these cytokines can be regulated by the active (secreted) form of IL-1β [26], suggesting that IL-1β plays a critical role in melanoma pathogenesis.

2.2. Melanoma and IL-1

IL-1β is a pleiotropic pro-inflammatory cytokine involved in cell proliferation, differentiation, tissue regeneration and immune regulation [26]. In addition, IL-1β is a tumor-promoting factor [11,27–33], immunosuppressive factor [12,34] and chemoresistant factor [35–37], that is strongly implicated in cancer progression [9,20,38]. Tumor cells secreting IL-1β have a greater propensity for invasion, angiogenesis, and metastasis [12,34].

Melanoma-derived IL-1β and its downstream intermediates are biologically active as autocrine and paracrine factors, markedly enhancing synthesis of IL-1 in melanoma cells, and mediating macrophage recruitment and angiogenesis *in vitro* [20]. IL-1β has also been shown to maintain survival and proliferation of melanoma and host stromal cells including macrophages and immune suppressor cells *in vivo* [5,12,34,39–41]. IL-1β thus promotes tumor cell invasion and metastasis [11,30–33]. Our recent work additionally suggests that as melanoma progresses, IL-1β secretion becomes increasingly autonomous [20].

2.3. Melanoma and the tumor microenvironment

Tumor microenvironment can influence complex biological processes such as tumor initiation, propagation and progression by affecting interactions of tumor cells with extracellular matrix proteins and/or stromal cells. Tumor microenvironment contains both tumor cells and stromal cells (such as macrophages and myeloid-derived cells). Tumor-associated macrophages have several tumor-promoting functions and are considered to be key regulators of the link between inflammation and cancer [39–41]. Myeloid-derived suppressor cells (MDSCs) recruit T regulatory cells to downregulate immune surveillance and antitumor immunity, thereby facilitating tumor growth [5,12,34].

Apte and his group investigated the role of host-derived and tumor-derived IL-1 as a regulator of tumor invasiveness [11,12]. B16 murine melanoma cells were injected into C57BL/6 wild type (WT), IL-1α, or IL-1β knockout (KO) mice. In IL-1α KO mice, tumorigenicity and angiogenesis were markedly reduced by 50% compared with those in WT mice, and in IL-1β KO mice, no tumor was developed. These findings suggest the importance of host-derived IL-1, particularly IL-1β, for invasiveness and angiogenesis of B16 melanoma cells [11]. Next, they transfected murine fibrosarcoma cells (which produce no IL-1α or IL-1β) with precursor IL-1α, mature IL-1β or IL-1β fused to a signal peptide (ssIL-1β), and tumorigenicity was assessed in WT mice. Only ssIL-1β transfectants secreted IL-1 and developed lung metastases, suggesting the importance of tumor-derived IL-1β secretion for invasiveness [12].

In the epidermis, melanoma cells are surrounded by keratinocytes and immune cells that produce and secrete IL-1α and IL-1β. Stimulants of non-microbial origin such as stress factors, neurosubstances, cell matrix, lipids and cytokines can stimulate transcription of IL-1 family and induce IL-1β secretion from these stromal cells [38]. IL-1 itself is a good inducer of its own gene expression in human macrophages/monocytes [42–44], endothelial cells [45], and vascular smooth muscle cells [46]. We have found that IL-1 is a better stimulant than LPS for IL-1β production and secretion in melanoma cells whereas LPS is a better stimulant for monocytic cells.

In addition to IL-1, other cytokines also play a role in the interaction between melanoma and the tumor microenvironment. IL-6 is a bi-functional cytokine, inhibiting the growth of normal melanocytes and early stage melanomas but augmenting the growth of advanced melanomas [47]. Paracrine effects of IL-6 involve the influence of tumor angiogenesis and alteration of the activity of tumor infiltrating immune cells [47]. IL-8/CXCL8, a CXC chemokine, recruits neutrophils and endothelial cells [48]. IL-8 is also an autocrine growth factor by promoting melanoma growth [49], and a paracrine growth factor by enhancing and stimulating angiogenesis [50]. MCP-1/CCL2 plays an important role in tumor microenvironment by recruiting monocytes/macrophages [51], NK cells and subpopulation of T cells, and stimulating monocytes to produce IL-1 and IL-6 but not TNF-α [52]. Of note, these cytokines can be induced by the active (secreted) form of IL-1β [26].

3. Biology of IL-1

3.1. IL-1 signal transduction and its biologic effect

The IL-1 gene family contains two major agonistic molecules (IL-1α and IL-1β) and one antagonistic cytokine, the IL-1 receptor antagonist (IL-1Ra) [14,38,53]. When secreted, IL-1β binds to IL-1 receptor I (IL-1RI) and heterodimerizes with IL-1R accessory protein, triggering the IL-1 signaling pathway [14,53]. An intracellular adaptor molecule, myeloid differentiation factor 88 (MyD88), phosphorylates IL-1R through its cytoplasmic Toll/IL-1 receptor (TIR) domain, activating interleukin-1 receptor associated kinases (IRAKs) and TNF-receptor-associated factor (TRAF)-6, leading to the activation of specific MAP kinases and NF-κB [54–57]. NF-κB then translocates to the nucleus and initiates the transcription of a series of pro-inflammatory genes. Among the many cytokines and chemokines