

Editorial

IL-1 in Th17 Differentiation and Inflammatory Tissue Damage

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Abstract

Interleukin-1 (IL-1) is produced by innate immune cells in response to both exogenous and endogenous “danger” signals. IL-1 acts on target cells to alter their gene expression profile, which leads to various functional consequences of the cells. In the immune system, IL-1 is a major mediator that connects innate and adaptive immune responses. Recent studies have shown that IL-1 acts directly on CD4 T cells to modulate T helper cell immune responses. It can also collaborate with cytokines released by the T cells to induce tissue damage under autoimmune conditions. Under inflammatory conditions lacking adaptive autoimmune components, IL-1 also induces tissue damages. The effects of IL-1 can be negatively regulated by IL-1 receptor antagonist, making it a promising tool for modulating immune and inflammatory responses in various pathological conditions.

Introduction

How innate immune system regulates adaptive immune responses has been a major focus of immunological research. The fundamental importance of this topic in immunology is highlighted by the recent studies that demonstrate the key role of the interactions between pathogen-associated molecular patterns and the toll-like receptors in the initiation of the adaptive immune responses. However, the study of the innate immune responses has a much longer history. Interleukin-1 (IL-1) was identified 40 years ago as “endogenous pyrogen” released by leukocytes in response to endotoxin stimulation [1]. More recent studies have discovered that IL-1 can directly regulate T helper cell responses, particularly Th17 response, and cause tissue damages in many inflammatory conditions both with and without adaptive immune components. This review attempts to highlight some important findings from these studies.

Basic biology of IL-1

There are two IL-1 molecules IL-1 α and IL-1 β that have largely identical functions [2]. Mature IL-1 α and IL-1 β molecules are generated by cleavage of pro-IL-1 α and pro-IL-1 β by calpain and caspase-1, respectively [3,4]. In addition to calpain, more recent studies have shown that other proteases, including granzyme B, elastase and chymase, can also process IL-1 α , and the proteolysis enhances the biological activities of IL-1 α [5]. Pro- and mature IL-1 α are primarily membrane anchored, but they can be released to extracellular space upon cell death as a component of the cytosolic contents or on membrane fragments [6]. In contrast, mature IL-1 β is secreted. The secretion of IL-1 β is induced by inflammatory stimuli including microbial pathogen-associated molecular patterns (PAMPs) and endogenous “danger” signals, e.g. ATP and uric acid crystals, released by stressed or damaged cells. These stimuli trigger the intracellular “danger” receptor NLRP3 inflammasome to activate caspase-1, which in turn cleaves pro-IL-1 β to produce mature IL-1 β

[7-9]. The inflammasome-activated production of IL-1 β is negatively regulated by autophagy. The activation of autophagy by Toll-like receptor ligands also targets pro-IL-1 β to autophagosome for degradation [10]. Conversely, disruption of autophagy facilitates the release of IL-1 β [11]. Extracellular IL-1, including Pro-IL-1 α , IL-1 α and IL-1 β , can bind to IL-1RI [12]. Conformational change induced by the ligand binding triggers the recruitment of IL-1 receptor accessory protein (IL-1RAcP) to the receptor, which is essential for IL-1 signaling [13]. Further signal transduction results in the formation of a multi-protein signaling complex that include MyD88 and IRAK4. A cascade of signaling events ultimately leads to the activation of NF- κ B and mitogen-activated protein kinases (MAPK) that alter gene expression profiles of the host cells [14]. Apart from the receptor-mediated signaling, the propeptide region of pro-IL-1 α contains a nuclear localization signal so that in many cell types pro-IL-1 α is predominantly localized in the nucleus [15,16]. Intranuclear pro-IL-1 α functions independently of IL-1RI [17]. Several studies have shown that intranuclear pro-IL-1 α enhances IL-6 expression [18,19]. Intranuclear pro-IL-1 α has also been shown to inhibit cell proliferation and induce apoptosis in some cases [20,21], but promote cell proliferation in others [22]. However, since IL-1 β is the primary extracellular form of IL-1, data discussed in the following sections are mostly generated from studies using IL-1 β .

Effects of IL-1 on Th17 cell differentiation

Extracellular IL-1, mainly IL-1 β , plays important role in Th17 differentiation. In humans, IL-1 in combination with IL-6 and/or IL-23 induced Th17 differentiation from naïve precursors [23,24]. In mouse, *in vitro* Th17 differentiation from naïve conventional CD4 T (CD4 Tcon) cells is induced by IL-6 and TGF- β [25]. However, more recent studies showed that *in vivo* IL-6 is required for Th17 differentiation only in the mucosa and skin but not in spleen and liver. In contrast, IL-1 is indispensable for *in vivo* Th17 differentiation in all tissues [26]. Multiple mechanisms may be responsible for the role of

IL-1 in Th17 differentiation. In human, IL-1 induces the expression of ROR γ t, the master transcriptional regulator for Th17 differentiation, in naïve CD4 T cells [24]. In mouse, *in vitro* studies showed that IL-1 primarily stimulates the expansion of Th17 cells and the expression of IL-17 [27-29], whereas the expression of ROR γ t appears not affected by IL-1 signaling [27]. Th17 cells play a critical role in the pathogenesis of experimental allergic encephalomyelitis (EAE). Consistent with the positive role of IL-1 in Th17 differentiation, IL-1RI^{-/-} mice were resistant to EAE [30]. Similarly, caspase 1^{-/-} mice, whose ability to produce mature IL-1 β were impaired, had reduced incidence and severity of EAE [31]. In addition to Th17 differentiation, IL-1 exerts a similar effect in stimulating the Antigen-driven expansion of Th1 and Th2 cells [32]. More information on the roles of IL-1 in Th1 and Th2 Cell differentiation can be found in a recent review by Santarlasci et al. [33].

The role of IL-1 in tissue damage in inflammatory conditions

Autoimmune conditions refer to inflammatory conditions that are initiated by adaptive immune responses. Not only does IL-1 play critical roles in shaping the adaptive immune response by regulating T helper cell differentiation, it also collaborates with cytokines produced by T helper cells to induce apoptosis to cause tissue damages. Many studies have shown that in type 1 diabetes (T1D), IL-1 can synergize with IFN- γ produced by pancreatic antigen-reactive Th1 cells to induce apoptosis in pancreatic β cells [34,35]. More recently similar synergistic effect has also been reported between IL-1 and IL-17 produced by Th17 cells [36]. While the mechanism for the collaboration of IL-1 and IL-17 is not well understood, considerable details have been learnt about the collaboration between IL-1 and IFN- γ . Exposure of b cells to IL-1 β and IFN- γ activates the MAPK/JNK hence its target c-Jun, which up regulates the expression of the apoptosis sensitizer DP5 [37,38]. DP5 binds and deactivates pro-survival factor Bcl-XL. Bcl-XL functions to sequester the apoptosis activator Puma. Thus, deactivation of Bcl-XL by DP5 releases Puma [39]. In addition, IL-1 and IFN- γ induce the synthesis of nitrite oxide (NO) that triggers ER stress [40]. ER stress up regulates DP5 and Puma [37,41], and suppresses the translation of the pro-survival factor Mcl-1 [42]. Like Bcl-XL, Mcl-1 sequesters Puma, therefore down-regulation of Mcl-1 further facilitates the release of Puma. Once released, Puma binds and activates pro-death protein Bax, which leads to the release of cytochrome c from mitochondria that starts the cascade of caspase activation [43]. Importantly, IL-1 also plays an important role in tissue damage caused by inflammation with apparent adaptive immune components, for example, b cell death in type 2 diabetes (T2D). In contrast to T1D, T2D is not considered as an autoimmune disease. Nonetheless, high glucose levels in T2D can stimulate IL-1 β Production by pancreatic β cells. Such b cell-derived IL-1 has a suicidal effect on the b cells by inducing b cell apoptosis through Fas expression [44]. IL-1 is a major cytokine found in the acute inflammation during Ischemia-reperfusion (I/R) [45], and is responsible for the apoptosis of various tissue parenchymal cells in I/R injury, most notably the death of cardiomyocytes [46,47]. Although the details of the mechanism have not been fully elucidated, it appears that under these circumstances IL-1 ultimately induces the expression of Bax and Bak to activate the mitochondrial apoptosis pathway [47,48].

Negative control of the effects of IL-1 by IL-1Ra

IL-1 signaling and its biological effects can be inhibited by IL-1R antagonist (IL-1Ra), a naturally produced protein of the IL-1 family [2]. IL-1Ra includes secreted and intracellular isoforms [49]. The secreted IL-1Ra binds to IL-1RI but does not recruit IL-1RAcP to the receptor, thereby competitively inhibits receptor dependent IL-1 signaling [50]. Thus, the biological functions of IL-1Ra 3 are to counterbalance those of IL-1. Consistent with the effect of IL-1 on Th17 differentiation discussed above, IL-17 production was elevated in IL-1Ra^{-/-} mice [51-53]. In addition, the IL-1Ra^{-/-} mice developed spontaneous arthritis, the severity of which is closely correlated with the levels of IL-17 expression [51]. These mice are also more susceptible than wild type mice to the induction of EAE in the absence of pertussis toxin [53]. Pertussis toxin is known to mimic the actions of IL-1 such that it serves to overcome the effect of IL-1Ra in the induction of EAE in the wild type mice. IL-1Ra is naturally expressed in the b cells in healthy individuals. Its expression is reduced in type 2 diabetic patients, and down-regulation of IL-1Ra by siRNA increases b apoptosis [54]. Conversely, anakinra, the clinically approved recombinant human IL-1Ra, protects b cells from apoptosis induced by high glucose or IL-1 plus IFN- γ [54,55]. Similarly, IL-1Ra expression was induced in ischemic cardiomyocytes as a protective mechanism [56,57]. Indeed, transfection of cardiomyocytes with IL-1Ra gene and administration of anakinra have both been shown to protect cardiomyocytes from I/R induced apoptosis [47,58]. Interestingly, not only the secreted IL-1Ra can attenuate IL-1 induced apoptosis, intracellular isoform IL-1Ra can also inhibit apoptosis of ischemic cardiomyocytes by directly binding and preventing the activation of caspase 9 [48].

Conclusion

IL-1 has emerged as a positive regulator of the adaptive immune responses, particularly the T helper cell immune responses. As the T helper cells are critically involved in many immunological diseases such as autoimmune diseases, IL-1 is an important target for controlling the pathological immune responses under such conditions. In addition to the immune regulatory functions, IL-1 alone or in collaboration with other cytokines can directly induce apoptosis of tissue parenchymal cells. Conditions where IL-1 induces tissue damages include both autoimmune diseases with active adaptive immune components and inflammatory conditions without apparent adaptive immune components. Therefore dampening IL-1 activity, such as by IL-1Ra, is beneficial for these conditions.

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