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Review

Role of Antigen-Presenting Cells in Innate Immune System

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Abstract. Activation of antigen-presenting cells (APC) and natural killer (NK) cells initiates the production of various proinflammatory cytokines including interleukin 12 (IL-12), interferon γ (IFN-γ) and nitric oxide (NO), which are important in the innate immune response for controlling infection by intracellular pathogens. In this review, we focus on these cytokines produced by APC and summarize the current understanding of how APC functions are regulated by cytokines in innate immunity.

Key words: dendritic cells; macrophages; IL-12; IL-15; IFN-γ; NO; γ_c; IL-2/15Rβ.

Introduction

The innate immune system is thought to have predated the adaptive immune response. Indeed, innate host defense mechanisms are found in all multicellular organisms, whereas adaptive immunity is found only in vertebrates. Interleukin 12 (IL-12), which is produced by antigen-presenting cells (APC) upon infection by micro-organisms, is a critical cytokine for triggering innate immune responses. Likewise, IL-12 production is a prerequisite for the activation of T helper type 1 (Th1) cell-mediated type 1 immune responses in adaptive immunity (Fig. 1)[29, 39, 60]. One of the most distinctive and important activities of IL-12 is its ability to induce interferon γ (IFN-γ) production by multiple cell types including natural killer (NK) cells and APC in innate immunity, and Th1 cells in adaptive immunity. In contrast to IL-12 and IFN-γ, IL-10 and several other cytokines antagonize these pathways by blocking IL-12 production[7, 24]. In fact, studies using neutralizing antibodies against IFN-γ and mice deficient for IL-12, IFN-γ, or IL-10 have documented the essential roles of these cytokines in controlling the resistance against intracellular pathogens including bacteria, fungi and protozoa[7, 10, 13, 24, 28, 37, 63]. IFN-γ produced by the effect of IL-12, in turn, acts on macrophages to express inducible NO synthase (iNOS) essential for nitric oxide (NO) production (Fig. 1). NO is one of the important effector molecules to eradicate infecting microbes. For example, in the absence of iNOS activity, IL-12 was unable to prevent the spread of *Leishmania* parasites[15, 16]. IFN-γ is thus an important cytokine, playing a major role in activating macrophages to kill infecting micro-organisms.

Abbreviations used: DC – dendritic cells, IL – interleukin, NO – nitric oxide, γ_c – cytokine common gamma subunit, Th1 – T helper type 1, APC – antigen-presenting cells, iNOS – inducible nitric oxide synthase, IRF – interferon regulatory factor.

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APC as Major IFN-γ Producers in Innate Immune Responses

NK cells have been considered to be major producers of IFN-γ in an early stage of infection. Studies with various microbes, including *Listeria monocytogenes*, *Toxoplasma gondii* and *Leishmania major*, revealed that IL-12 derived from dendritic cells (DC) and activated macrophages stimulates NK cells to produce IFN-γ[29, 39, 60]. Several studies indicated, however, that IFN-γ is also produced by APC, including macrophages and DC. Murine[14, 23, 40, 45, 56] or human[19] macrophages produce IFN-γ in response to various stimuli such as LPS[23], IFN-γ[14], *L. monocytogenes*[56], IL-12[45], IL-12 plus IL-18[40], and *Mycobacterium tuberculosis*[19]. Since IFN-γ is one of the most potent up-regulators of IL-12, MHC class II, CD40 and iNOS expression in macrophages, it is possible that IFN-γ produced by macrophages is involved as a critical cytokine in an autocrine activation pathway (Fig. 2)[40]. In addition, IFN-γ prevents apoptotic death of macrophages by inducing p21^{waf1} and arresting their cell cycles[65].

The other type of APC capable of producing IFN-γ is DC. DC are the most efficient APC to activate naive T cells. Endocytosis and the processing of antigens by immature DC allow them to mature with the ability to migrate into T cell area of secondary lymphoid organs[6, 12]. Upon maturation, they lose their ability to capture and process antigens, but, instead, they express high levels of MHC class II molecules loaded with antigenic peptides and costimulatory molecules, such as CD40, CD80, and CD86. Consequently, naive T cells are activated by recognizing peptide/MHC complexes and express CD154 at a high level. Activated T cells, in turn, activate DC through CD40-CD154 interaction[48]. CD40--CD154 interaction is also important in the survival of DC in T cell areas. In mice, there are at least two different types of DC[57, 61, 62, 64]. They differ in surface phenotype, origin (myeloid versus lymphoid), the cytokine required for their development (GM-CSF versus IL-3), and biological function. Recent studies indicated that CD8α$^+$ lymphoid DC (LDC) are able to induce a Th1 response, whereas CD8α$^-$ myeloid DC (MDC) induce a Th2 response[38, 46, 55]. In addition, it has been reported that DC derived from Peyer's patches (PP)[30] and the liver[33], but not from the spleen, were found to prime naive T cells for the production of IL-4 and IL-10, both of which are Th2 cytokines. These results suggest that DC of different origin and those residing in different tissues are capable of inducing distinct immune responses.

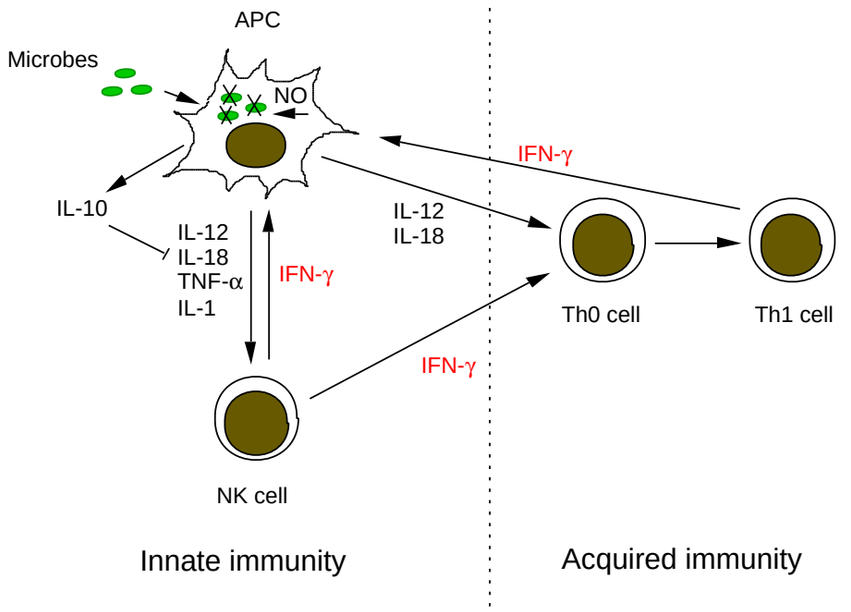

Fig. 1. Innate immunity and Th1 differentiation. Activation of macrophages and DC by infectious agents leads to secretion of IL-12, which subsequently induces IFN-γ production by NK cells and directs Th1 development. IFN-γ, in turn, acts on monocytes to augment IL-12 secretion and to produce NO, which eradicates infecting microbes. Thus, IL-12 and IFN-γ comprise a positive feedback system

We and others have recently demonstrated that mature DC express IL-12 receptors[27, 44] and are capable of producing significant amounts of IFN-γ in an IL-12-dependent manner[44]. The amounts of IFN-γ from DC and macrophages are much higher than those from NK cells[44]. Although IL-12 and IFN-γ are produced by both LDC and MDC, LDC are the major producers of IL-12 and IFN-γ[38, 44]. IL-2, IL-4 and IL-18 augment IL-12-dependent IFN-γ production by mature DC[21, 22]. It should be noted that DC are able to produce IL-12 and IFN-γ during antigen presentation as a result of CD40-CD154 interaction[21], implying the importance of DC-derived IL-12 and IFN-γ in Th1 development during antigen presentation. Since IL-12 is produced by DC independently of T cells[52], DC-derived IL-12 triggers an autocrine activation pathway between IL-12 and IFN-γ as described in macrophages[22, 27, 44] (Fig. 2).

Like murine DC, human DC are classified into at least two subpopulations, namely DC1 (myeloid DC) and DC2 (lymphoid DC). Contrary to murine DC, it appears that DC1 and DC2 induce Th1 and Th2 responses, respectively[49]. Upon CD40 ligation, DC1 produce IL-1, IL-6, IL-8, IL-10 and IL-12, whereas DC2 secrete IL-8 but not other cytokines tested[49]. Precursors of DC2 produce high levels of IFN-α/β upon viral infection, suggesting that this population plays a critical role in the acute phase of viral infection[54]. In both the human and mouse, DC can be generated from $CD34^+$ bone-marrow precursors[11, 51] and $CD14^+$ monocytes with GM-CSF in combination with TNF-α or IL-4[66]. These cells, however, secrete little amount of IFN-γ[47] (our unpublished data). It is possible that only a subpopulation of DC produce IFN-γ, depending on their origin and the location where the DC reside, as discussed above. Alternatively, it is possible that employment of cytokines during the differentiation of DC artificially down-regulates the ability of DC precursors to produce IFN-γ. Human DC freshly prepared without any cytokine supplement should be tested for their ability to produce various cytokines, including IFN-γ.

The Role of a Cytokine(s) Utilizing a γ_c-Mediated Signaling System in APC Functions

The previous conclusion that NK cells are the major IFN-γ producers was drawn from the observation that $\gamma_c^{-/-(Y)}$ Rag-$2^{-/-}$ mice lacking all lymphoid cells including NK cells, produce minimal amounts of IFN-γ[3]. Although DC and macrophages are normally present in $\gamma_c^{-/-(Y)}$ Rag-$2^{-/-}$ mice[4, 50], their IFN-γ production in response to IL-12 is impaired[44], suggesting the importance of γ_c-mediated signaling in the functional maturation of DC and macrophages.

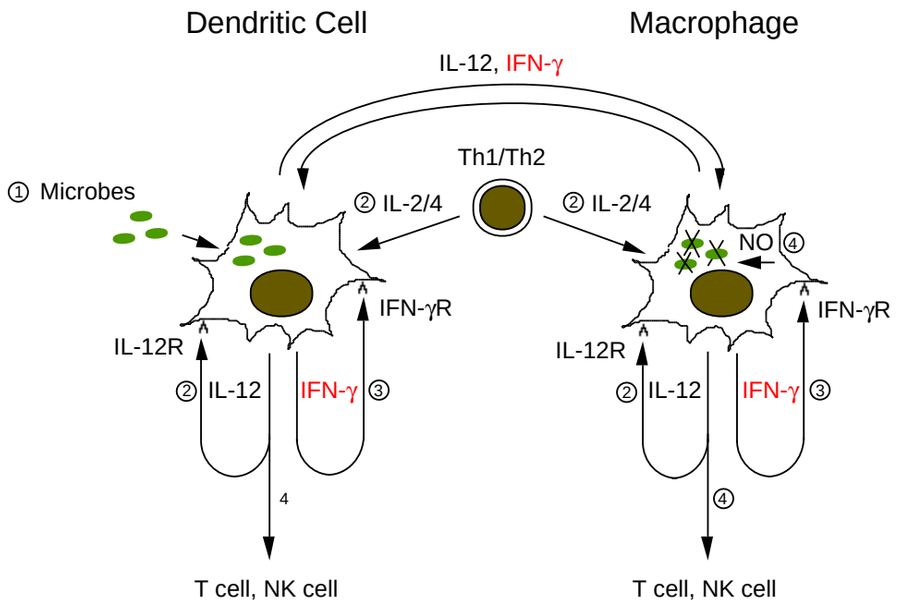

Fig. 2. Autocrine APC activation pathway. DC produce IL-12 and IFN-γ in an autocrine manner when triggered by microbial infection. Once IL-12 and IFN-γ are produced by DC, a positive feedback pathway(s) is activated between DC and macrophages, even in the absence of NK cell-derived IFN-γ. Macrophages then secrete IFN-γ in response to IL-12, which also activates macrophages in an autocrine manner to produce NO. IL-2 and IL-4 augument such IL-12-dependent IFN-γ production by APC

There are at least five cytokines utilizing γ_c as a subunit of their receptor components. These are IL-2, IL-4, IL-7, IL-9 and IL-15. Among them, IL-2 and IL-15 share another subunit in their receptor systems, namely the IL-2/15Rβ subunit. IL-2/15Rβ$^{-/-}$Rag-2$^{-/-}$ mice also showed phenotypes similar to those of $\gamma_c^{-/-(Y)}$ Rag-2$^{-/-}$ mice (unpublished data), suggesting that either IL-2 or IL-15 is critical in the functional maturation of APC.

Recently, two groups independently generated mice deficient in IL-15Rα[34] and IL-15[32], and demonstrated the critical role of the IL-15/IL-15R system in the development of NK cells. Interestingly, IL-15 type-1 receptors, consisting of IL-15Rα, IL-2/15Rβ and γ_c, are expressed not only on NK and T cells, but also on APC, such as DC and macrophages[2, 8, 17, 21, 26, 31], implying the physiological importance of the IL-15/IL-15R system in APC functions. Indeed, IL-15 is required for LPS-induced TNF-α production by macrophages[1]. These studies collectively indicate that IL-15/IL-15R interaction is critical in the early activation of APC. Other studies, using neutralizing antibodies against IL--15[18] and transgenic mice expressing a dominant-negative form of IL-15[42] also suggested that the effect of IL-15 on IFN-γ induction overlaps with that of IL-12. As impaired IL-12 production has also been observed in mice deficient for interferon regulatory factor (IRF)--1[35, 59], nuclear factor κB (NFκB)[41], IFN consensus sequence-binding protein (ICSBP)[9, 25, 53], Mkk3[36], or Eta--1[5], one of these molecules may function downstream of the IL-15 receptor.

In humans, patients with X-linked severe combined immunodeficiency disease (XSCID) have mutations in the γ_c gene[43, 58]. XSCID is characterized by severe impairment of cell-mediated type-1 immune responses. Our findings of APC defects in mice the lacking γ_c gene, an animal model of human XSCID, indicate that the impairment of APC functions is another possible factor which may deal a fatal blow to $\gamma_c^{-/-(Y)}$ mice and, likewise, to patients with XSCID upon infection by micro-organisms.

Conclusion

Acquired immunity, mediated by T and B cells recognizes foreign antigen and eventually clears infecting micro-organisms. In contrast, the innate immune system, composed of APC and NK cells, suppresses microbial growth at an early stage of infection and determines the functional outcome of most responses to pathogens. Autocrine APC activation would thus be important especially in the early stage of infection (Fig. 2), and IL-15 is a potential cytokine governing such innate immune responses by regulating the early activation of APC and NK cell development.

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