The International Journal of Biochemistry & Cell Biology 40 (2008) 2379–2383

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

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

Signaling networks in focus

Interleukin 27 signaling pathways in regulation of immune and autoimmune responses

Hiroki Yoshida*, Yoshiyuki Miyazaki

Division of Molecular and Cellular Immunoscience, Department of Biomolecular Sciences, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan

ARTICLE INFO

Article history:
Received 19 March 2008
Received in revised form 7 May 2008
Accepted 13 May 2008
Available online 8 June 2008

Keywords:
Interleukin 27
Helper T cell
Autoimmune disease
IL-10

ABSTRACT

Cytokine-mediated immunity plays a crucial role in pathogenesis of various diseases including autoimmune disease. Recently, interleukin 27 was identified, which along with interleukin 23 belongs to the interleukin 12 cytokine family. Interleukin 27 is pivotal for the induction of T helper 1 responses. Recent studies, however, revealed that interleukin 27 has an immunosuppressive property. In interleukin 27 receptor-deficient mice, various pro-inflammatory cytokines were over produced resulting in excess of immune responses. The immunosuppressive effects of interleukin 27 depend on suppression of interleukin 2 production, inhibition of the development of T helper 17 cells (a newly identified inflammatogenic T helper population), and induction of interleukin 10 production. Activation of signal transducers and activators of transcription 1 and 3 is critical in the immunosuppressive function of interleukin 27. Interleukin 27 suppresses some diseases of autoimmune or allergic origin, demonstrating its promising potential in therapy of diseases mediated by inflammatory cytokines.

- IL-27 is critical in initial Th1 differentiation via STAT1-mediated T-bet activation.
- IL-27 suppresses production of a group of pro-inflammatory cytokines by T cells.
- IL-27 also suppresses differentiation of Th17 cells, a newly identified helper T cell subset that produces IL-17. IL-27 induces IL-10 production by activated T cells for its anti-inflammatory effects.
- Activation of STAT1 and 3 is important for IL-27-mediated immunosuppression.

1. Introduction

Cytokines are critical players in the pathogenesis of various diseases. With the help of various cytokines, immune cells undergo proliferation, activation, differentiation, and inactivation or cell death. By sharing receptor subunits and signal-transducing molecules, many cytokines are known to play redundant and occasionally pleiotropic roles in immune responses. Among various types of cells involved in immune responses, $CD4^+$ T cells play critical roles in immune regulation. To date, it has been understood that naive $CD4^+$ T cells differentiate into two distinct subsets; T helper (Th) 1 cells for cellular immunity and Th2 cells for humoral immunity. Recent discoveries, however, of $CD4^+$ T cell subsets Th17 and Treg with distinct characteristics including revealed unprecedented diverse functions of $CD4^+$ T cell. By determining the $CD4^+$ T cell differentiation, cytokines initiate, direct, maintain, and even attenuate/terminate the immune responses.

Abbreviations: Th, helper T cell(s); IL, interleukin; IFN, interferon; STAT, signal transducer and activator of transcription; TNF, tumor necrosis factor; TGF, transforming growth factor; EAE, experimental autoimmune encephalomyelitis; GN, glomerulonephritis; iTreg, induced regulatory T cell.

* Corresponding author. Tel.: +81 952 34 2290; fax: +81 952 34 2062.
E-mail address: yoshidah@med.saga-u.ac.jp (H. Yoshida).

1357-2725/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.biocel.2008.05.020

2. Functions

Interleukin (IL-) 12 was identified as a potent inducer of interferon (IFN-) γ production by T cells, natural killer cells, and other types of lymphocytes, and was shown later to be an essential inducer of Th1 differentiation. Since its discovery, IL-12 had been the only known heterodimeric cytokine, composed of two subunits, p35 and p40. Recently, however, IL-23 and IL-27 were identified as heterodimeric cytokines structurally related to IL-12. IL-23 is a heterodimeric cytokine composed of the p40 subunit of IL-12 and p19, an IL-12p35-related molecule. IL-27 is another heterodimeric cytokine composed of EBI-3, a p40-related molecule, and p28, a p35-related molecule. Along with IL-35 composed of p35 and EBI-3, and two other cytokines, IL-12, 23, and 27 compose a family of heterodimeric cytokines.

2.1. Th1-initiating trait of IL-27 and its receptor, WSX-1

IL-27 is a key cytokine to drive naive cells into Th1 subset at the initial step of differentiation. The role of WSX-1, the α subunit of IL-27 receptor (R) complex, in Th1 differentiation was analyzed in WSX-1-deficient (*WSX-1*$^{-/-}$) mice. In two independent reports by us (Yoshida et al., 2001) and by Chen et al. (2000), *WSX-1*$^{-/-}$ mice, as compared with wild-type mice, showed impaired IFN-γ production and remarkable susceptibility to *Leishmania major* and *Listeria monocytogenes*, respectively, both intracellular pathogens whose clearance largely depends on Th1 response. Interestingly, impaired production of IFN-γ was observed only at early phases of *L. major* infection, and the IFN-γ production in *WSX-1*$^{-/-}$ mice was restored to the wild-type level at late phases of infection. Thus, IL-27/WSX-1 signaling is only required at the initial step of Th1 differentiation. Downstream of WSX-1, signal transducer and activator of transcription (STAT) 1 binds to the conserved tyrosine residue of the cytoplasmic portion of the receptor in a phosphorylation-dependent manner and is transcriptionally activated after IL-27 stimulation. This STAT1 activation leads to induction and activation of T-bet, the Th1-specific transcription factor. With the help of IL-27-induced T-bet activation, naïve T cells become responsive to subsequent IL-12 stimulation (Takeda et al., 2003). IL-27 helps Th1 differentiation also through T-bet-independent mechanisms.

2.2. The anti-inflammatory properties of IL-27/WSX-1

IL-27 also has an immunosuppressive function and suppresses production of inflammatory cytokines. When infected with *Trypanosoma cruzi*, an intracellular protozoa, *WSX-1*$^{-/-}$ mice produced more IFN-γ than wild-type mice and demonstrated cytokine-mediated liver damages during the infection (Hamano et al., 2003). In addition to IFN-γ, CD4$^+$ T cells isolated from *T. cruzi*-infected *WSX-1*$^{-/-}$ mice showed hyper production of other pro-inflammatory cytokines including IL-6 and tumor necrosis factor (TNF-) α. Similarly, *WSX-1*$^{-/-}$ mice were more susceptible to *Mycobacterium tuberculosis* with cytokine-mediated severe inflammation (Holscher et al., 2005). Similarly, *WSX-1*$^{-/-}$ mice demonstrated hyper production of various cytokines in allergen-induced airway hypersensitivity model or concanavalin A-induced hepatitis model as well. As expected, IL-27 suppressed cytokine production of activated T lymphocytes in vitro (Yoshimura et al., 2006). These results collectively revealed the novel role of IL-27/WSX-1 as an attenuator of pro-inflammatory cytokine production. This immunosuppressive role of IL-27 is particularly important to prevent the excess of inflammation that may result in fatal organ damage and/or subsequent autoimmune reaction.

IL-27/WSX-1 suppresses inflammation also by inhibiting differentiation of Th17 cells, a newly identified inflammatogenic Th subset that produces IL-17A/F, IL-6, 21, and 22, but neither IFN-γ nor IL-4 (Langrish et al., 2005). By producing a group of pro-inflammatory cytokines, Th17 cells are involved in various inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel diseases. In *WSX-1*$^{-/-}$ mice, encephalomyelitis of autoimmune origin (experimental autoimmune encephalomyelitis; EAE) or of infectious origin was exacerbated compared with wild-type mice, concomitant with augmented Th17 differentiation (Stumhofer et al., 2006; Batten et al., 2006). These reports demonstrated that IL-27/WSX-1 inhibits Th17 differentiation and thus may attenuate some inflammatory diseases of autoimmune origin. Actually, IL-27 effectively suppressed Th17 differentiation induced by IL-6 plus transforming growth factor (TGF-) β in vitro. This is in good contrast that IL-23, another IL-12-related cytokine, helps Th17 differentiation and the subsequent induction of inflammatory diseases. Interestingly, Neufert et al. reported inhibition of TGF-β-dependent development of induced regulatory T cell (iTreg) by IL-27 (Neufert et al., 2007). Thus, depending on context, IL-27 may up regulate immune responses by suppressing iTregs instead of suppressive total immune responses. IL-35, another IL-12 cytokine family member composed of p35 of IL-12 and EBI-3, also suppresses Th17 development (Niedbala et al., 2007). EBI-3 subunit, shared by IL-27 and IL-35, may be a key molecule for the Th17 suppression.

IL-27 also suppresses function of dendritic cells and macrophages (Wang et al., 2007). In addition to the aforementioned direct suppressive effects on T cells, down regulation of cytokine production and expression of accessory molecules by antigen-presenting cells may also represent an important indirect mechanism to modulate excessive T cell-mediated inflammation.

2.3. Key molecules

Villarino et al. reported that IL-27 suppressed IL-2 production of CD4$^+$ T cells (Villarino et al., 2006). WSX-1-deficient CD4$^+$ T cells produced more IL-2 than wild-type counterparts during in vitro differentiation. Since IL-12 has the same ability to limit IL-2 production, these two cytokines may inhibit T cell proliferation to presumably ensure proper differentiation of the cells by avoiding unnecessary cell activation.

More recently, it was reported that IL-27 induces IL-10 production of activated CD4$^+$ T cells (Stumhofer et al., 2007; Fitzgerald et al., 2007b; Awasthi et al., 2007). Interestingly, IL-27-induced IL-10 production of differentiated