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Mini review

Tyk2-mediated homeostatic control by regulating the PGE_2-PKA-IL-10 axis

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Abstract: Tyrosine kinase 2 (Tyk2), which associates with the receptors for type I interferon (IFN) and interleukins (IL)-6, IL-10, IL-12, and IL-23, is critical to mediate cytokine-induced signals. Tyk2 plays an essential role in the constitutive production of small amount of type I IFNs and in the promotion of differentiation from naïve T cells into Th1 or Th17 effector cells via IL-12- and IL-23-induced signals. Additionally, Tyk2-mediated signaling suppresses the *in vivo* production of IL-10, which is a strong anti-inflammatory cytokine. The elevated IL-10 production in the peritoneal cells of Tyk2-deficient mice are alleviated by treatment with either diclofenac, a cyclooxygenase inhibitor, or H-89, a protein kinase A inhibitor. Notably, significantly higher basal prostaglandin E_2 (PGE_2) production is observed in peritoneal cavity of Tyk2-deficient mice than that of wild-type mice. Phosphorylation of cAMP response element-binding protein, induced by *P. acnes* and PGE_2 addition, is upregulated in Tyk2-deficient macrophages. This indicates that higher IL-10 production in Tyk2-deficient mice is likely a result of the enhanced PGE_2-protein kinase A pathway. Thus, Tyk2-mediated signaling regulates multiple events during immune and/or inflammatory responses.

Keywords: Tyk2; cytokines; signal transduction; immune system; inflammation; PGE_2; PKA; IL-10; virus-induced diabetes

1. Introduction

The intracellular domains of receptors for cytokines and growth hormones constitutively

associate with selective Janus kinase family members (Jaks). Cytokine-binding to their receptors induces the auto-activation of Jaks. The activated Jaks then phosphorylate the intracellular tails of receptors, which in turn provide docking sites for the signal transducer and transcription activator (STAT). Receptor-localized STATs are then phosphorylated, resulted in their dissociation from the receptor and translocation into the nucleus, in which they drive gene expression as a result of cytokine stimulation [1,2]. Thus, the Jak-STAT signaling pathway is widely utilized by cytokine receptor superfamily members.

The Jak family is composed of four members and shares structurally similar functional domains. Both the 4.1, ezrin, radixin, moesin (FERM) homology domain and the atypical Src-homology 2 (SH2) domain facilitate protein-protein interactions. The pseudo-kinase domain negatively regulates the kinase activity. The catalytic activity of tyrosine kinase domain increases via trans- and/or auto-phosphorylation of the activation loop upon undergoing conformational changes of ligand-bound receptors [1,2].

Tyk2 was originally identified as a tyrosine kinase, which has the ability to compensate for a mutation that makes fibroblasts unresponsive to IFN-α [3]. Tyk2 has been implicated in both innate and acquired immune responses as it regulates the constitutive basal production of small amounts of type I IFNs as well as the elevation of numbers and activity of T helper 1 (Th1) and Th17 cells. Here, we describe the current knowledge on the impact of Tyk2-mediated signaling and its novel role in immune response via the regulation of the PGE_2-PKA-IL-10 axis.

2. The requirement of Tyk2 in the cytokine signaling

Jaks are associated with cytokines or growth factor receptors and activate STAT family proteins. Jaks are unique tyrosine kinases that contain both catalytic and pseudo-kinase domains with autoregulatory mechanisms [2]. Tyk2 associates with some heterodimeric cytokine receptor complexes, including IFNAR1, IL-12Rβ1, IL-10R2, and IL-23Rα1 [3–7]. IL-22, a central cytokine in tissue-barrier function, wound healing, and epithelial homeostasis and repair, recognizes receptors carrying IL-10R2. IL-12, that promotes cell-mediated immunity against infection and cancer, and IL-23, a key mediator of inflammation, bind to receptors carrying IL-12Rβ1. Both IFN-α and IFN-β, use receptors carrying IFNAR1. In addition, Tyk2 also associates with the gp130 receptor chain (Figure 1).

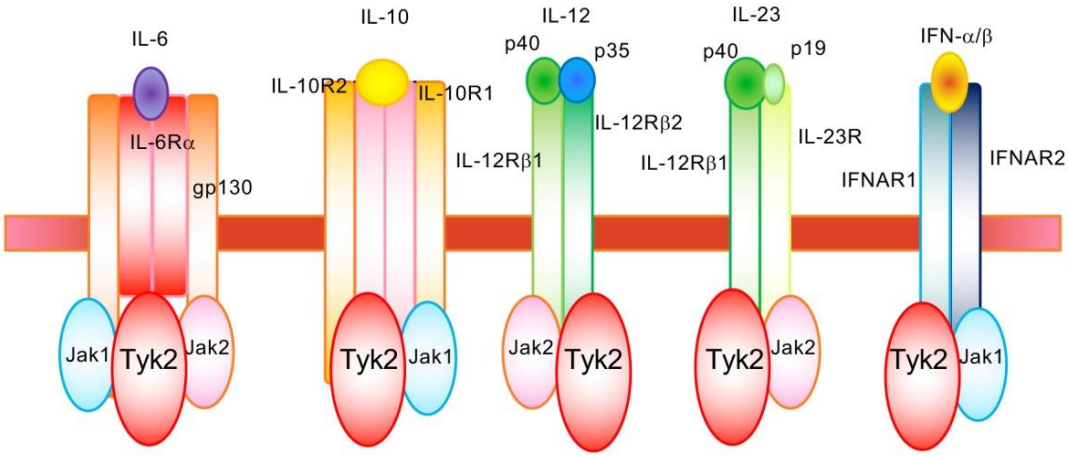

Figure 1. A schematic representation of the Tyk2-related cytokine receptors. The IL-6 receptor consists of two components, IL-6Rα (gp80) and IL-6Rβ (gp130), and associates with Jak1, Jak2 and Tyk2. The IL-10 receptor consists of two components, IL-10R1 and IL-10R2, and associates with Jak1 and Tyk2. IL-12 is a heterodimeric cytokine carrying IL-12p35 and IL-12p40 subunits. IL-12p40 subunit is also a component of IL-23 and dimerizes with IL-23p19 to form IL-23. The IL-12 receptor consists of IL-12Rβ1 and IL-12Rβ2, and the IL-23 receptor is composed of IL-12Rβ1 and IL-23R. Both receptors associate with Jak2 and Tyk2. The IFN-α/β receptor consists of IFNAR1 and IFNAR2 and associates with Jak1 and Tyk2.

Tyk2 has a limited concernment in the IFN-α signaling pathway; however, Tyk2-deficient mice demonstrate impaired lipopolysaccharide (LPS)-mediated nitric oxidase production as well as insufficient growth inhibition of B lymphocyte progenitors by IFN-α [8–11]. In contrast, IL-12 function, especially Th1 differentiation, is completely abrogated by Tyk2-deficiency [4,5]. Indeed, Tyk2-deficient mice show less severity of immune/inflammatory phenotypes in several murine experimental models, such as the arthritis and colitis models [6,12]. Notably, patients with a homozygous TYK2 mutation, which results in the absence of mature Tyk2 protein, develop autosomal recessive hyper IgE syndrome (AR-HIES), which is a primary immunodeficiency disorder characterized by elevated IgE serum levels, repeated onsets of skin abscesses, and recurrent pneumonia [13]. The patient also experiences atopic dermatitis-like skin inflammation that is caused by the accelerated Th2 differentiation [13]. In a Th2-mediated allergic airway inflammation model experiment, Tyk2-deficiency induced severe condition of the disease [14]. Therefore, Tyk2-mediated signals account for both innate and acquired immune systems, especially balance betweenTh1 and Th2 differentiation.

3. The involvement of Tyk2 in the production and function of Th1 and Th17 cells

IL-12 is a heterodimeric cytokine, which consists of covalently linked p35 and p40 subunits.

IL-12 p40 subunit is shared by IL-23 whose other subunit is a unique p19. IL-12 receptors associate with Tyk2 and Jak2 that mediate activation of STAT4 transcription factor. Combined signals from both phosphorylated STAT4 and T cell receptor induce the expression of T-bet, which acts as a master transcriptional factor for the differentiation of naive $CD4^+$ T cells into Th1 cells. Th1 cells promote cell-mediated immune responses to defend against viral or bacterial pathogens [15]. In addition, Th1 cells secrete IFN-γ, IL-2, and TNF-α that induce the activation of macrophages, production of nitric oxide, and proliferation of cytotoxic T cells. IL-23 receptors, which associate with Tyk2, induce signals for the functional maturation, proliferation, and maintenance of Th17 cells, although TGF-β and IL-6 are essential for the differentiation into Th17 cells. Th17 cells promote massive inflammatory responses to eliminate microbial pathogens through secretion of pro-inflammatory cytokines, such as IL-17, IL-21, and IL-22. However, excessive and prolonged activation of Th17 cells is sometime observed in human autoimmune and/or inflammatory disorders, such as inflammatory bowel diseases, rheumatoid arthritis, and psoriasis [16–18].

Tyk2 plays an essential role in immune responses mediated by both the IL-12/Th1 and IL-23/Th17 axis. Since both Th1 and Th17 cells actively promote pro-inflammatory responses, which are regulated by Tyk2-mediated signals, the mutations leading to the dysregulation of Tyk2 can induce striking immunological phenotypes [6].

Using Tyk2-deficient murine experimental models, our study have revealed the role of Tyk2 in driving pathological immune and/or inflammatory responses [6,12,19]. Tyk2-deficient dendritic cells fail to produce IL-12 and IL-23 and lose the ability to promote Th1 cell differentiation even when stimulated with CpG oligodeoxynucleotides [20]. In collagen-induced arthritis and anti-type II collagen antibody-induced arthritis models, Tyk2-deficient mice exhibit markedly low susceptibility to arthritis [12]. In an experimental autoimmune encephalomyelitis model, Tyk2-deficient mice exhibited lower clinical scores and few lymphocytes had infiltrated the inflamed central nervous system [19]. In dextran sulfate sodium-induced colitis and 2,4,6-trinitrobenzene sulfonic acid-induced colitis models, Tyk2-deficient mice exhibit slower and reduced disease development than wild-type (WT) mice [6]. Tyk2-deficient mice exhibit slower and reduced disease development than WT mice. In a skin inflammation model induced by imiquimod, a ligand for TLR7, Tyk2-deficient mice exhibit less epidermal hyperplasia, parakeratosis, and inflammatory cell accumulation [6,21]. On repeated injections of a specific protein antigen, Tyk2 is required to induce footpad swelling [6].

Therefore, Tyk2 modulates host defense by controlling the production and function of both Th1 and Th17 cells. Tyk2 knockdown is likely to decrease inflammatory phenotypes in murine experimental models (Figure 2).

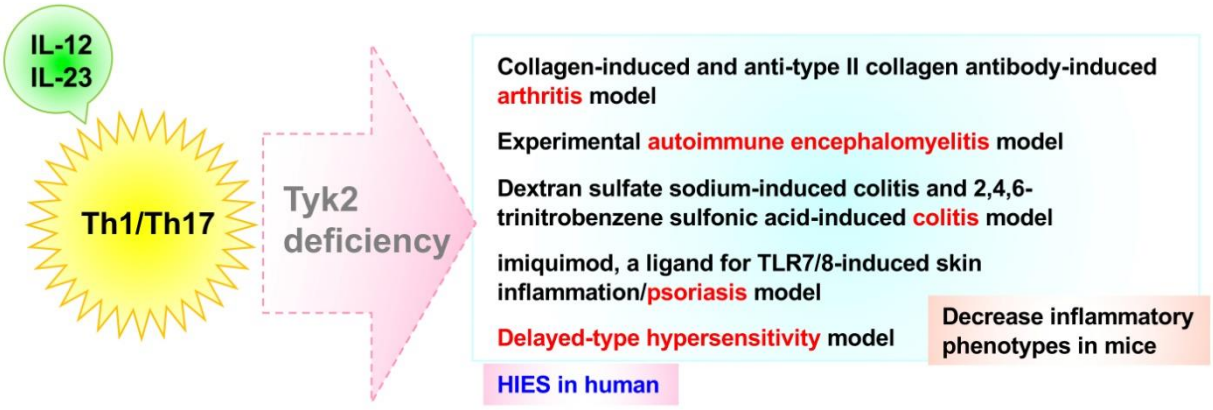

Figure 2. A schematic representation of involvement of Tyk2 in immune and inflammatory responses with the murine experimental models using Tyk2-deficient mice.

4. The involvement of Tyk2 in constitutively produced type I interferons

Type I IFNs are constitutively produced by various types of cells, such as macrophages. Although their constitutive expression is low, type I IFNs regulate normal cellular events in a paracrine or autocrine manner [22,23]. Mice with a deletion of *Ifnar1* gene fail to produce constitutive type I IFN and have less pro-inflammatory functions of macrophages through reduced capacity to express IFN-inducible inflammatory genes, such as *Cxcl10* [24]. Thus, spontaneous autocrine type I IFNs play an essential role in driving full responsiveness against IFN-α as well as IFN-γ [22,23]. Notably, Tyk2 contributes to constitutive basal IFN-α production by macrophages that are required for the innate immunity to eliminate bacterial components. In Tyk2-deficient macrophages, basal and LPS-induced IFN-α production is significantly impaired [8]. When Tyk2-deficient and IFN-β-deficient mice are treated with high doses of LPS, they show significant resistance to the lethal septic shock [9]. In addition, the expression of IFN-related genes is decreased in Tyk2-deficient macrophages, especially under steady-state conditions [10].

Therefore, Tyk2 contributes to the constitutive production of small amounts of basal type I IFNs, which regulates maximal immune cell function *in vivo*.

5. The involvement of Tyk2 in the regulation of the IL-10 production

Intraperitoneal injection of heat-killed *Propionibacterium acnes* (*P. acnes*) into mice induces acute inflammation in the peritoneal cavity, with massive neutrophil infiltration and granuloma formation [25,26]. Tyk2-deficient mice injected with *P. acnes* had a significantly lower number of infiltrated neutrophils, less pro-inflammatory cytokines, and more IL-10 concentration in the peritoneal cavity compared to WT mice [26]. IL-10 is a powerful anti-inflammatory cytokine, which has an ability to limit tissue injury by downregulating the duration and intensity of immune/inflammatory responses, and the production of IL-10 is known to in part require autocrine type I IFN signaling [24,27].

Although Tyk2 is involved in IFN production and signaling, pretreatment of WT mice with

neither anti-IFNAR1 nor anti-IFN-γ antibodies potentiate *P. acnes*-induced peritoneal inflammation. However, pretreating Tyk2-deficient mice with a neutralizing antibody against the IL-10 receptor significantly restored peritoneal inflammation by *P. acnes* to similar levels observed in untreated WT mice, suggesting that the elevated IL-10 is responsible for the suppression of inflammatory phenotype in Tyk2-deficient mice with *P. acnes*-injection. Therefore, Tyk2 is likely to regulate IL-10 production in an IFN-independent manner.

IL-10-producing macrophages in peritoneal cavity highly increase in Tyk2-deficient mice as compared with that in WT mice [26]. The numbers of IL-10-producing F4/80-negative or B220-positive cells are similar in the peritoneum between Tyk2-deficient and WT mice. Thus, macrophages seem to be a responsible cell population for elevated IL-10 production in Tyk2-deficient mice. Production of IL-10 by macrophages is known to be enhanced by prostaglandin E_2 (PGE_2) signaling, which induces protein kinase A (PKA) activity. Indeed, IL-10 production by peritoneal cells is greatly inhibited by the addition of diclofenac, which suppresses prostaglandin production by inhibiting cyclooxygenases. A specific PKA inhibitor H-89 also abrogates *P. acnes*-induced IL-10 production by peritoneal cells. Interestingly, the peritoneal lavage from steady-state Tyk2-deficient mice contains much more PGE_2 than that from WT mice, suggesting that the elevated production of IL-10 observed in Tyk2-deficient mice can be attributed to the immunosuppressive microenvironment established by high basal PGE_2 levels in peritoneal cavity.

The phosphorylation of cAMP response element binding protein (CREB), known as a hallmark of PKA activation, is induced by *P. acnes*-treatment alone and is further enhanced by exogenous PGE_2 administration. Tyk2-deficient bone marrow-derived macrophages show enhanced CREB phosphorylation after *P. acnes*-treatment alone as well as combined stimulation with *P. acnes* plus PGE_2. Thus, Tyk2 negatively regulates PKA activity induced by *P. acnes*-treatment.

Tyk2-deficiency makes macrophages act as anti-inflammatory cell populations because Tyk2-deficient macrophages have high potential to produce IL-10. Therefore, in *P. acnes*-induced peritoneal inflammation, Tyk2 downregulates the PGE_2-PKA-IL-10 pathway, resulting in a pro-inflammatory phenotype (Figure 3).

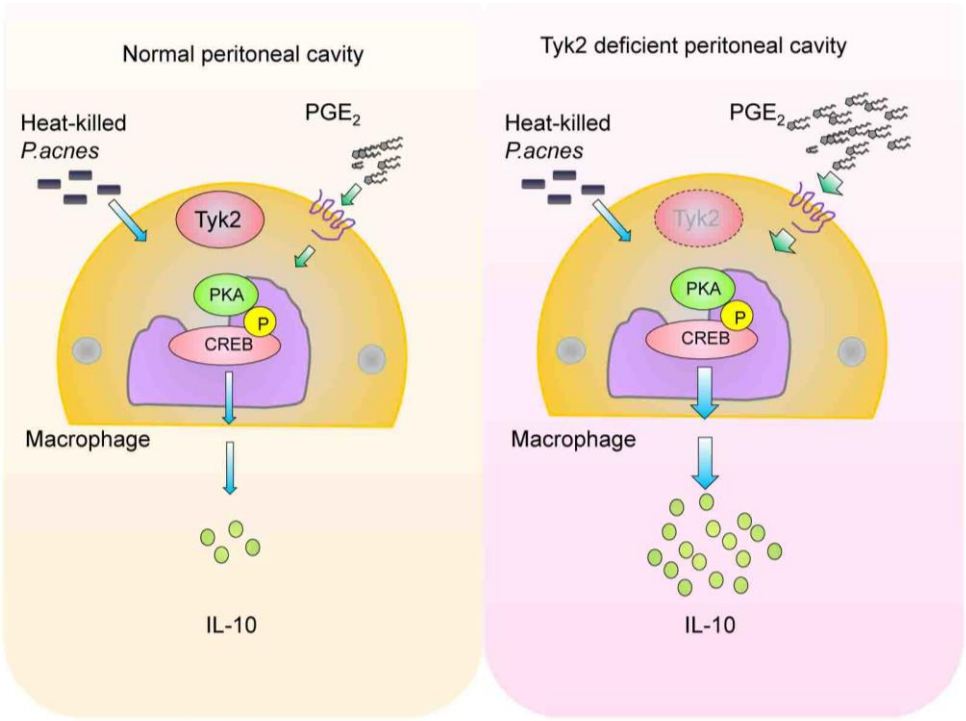

Figure 3. Tyk2 down-regulates the PGE_2-PKA-IL-10 pathway in the *P. acnes*-induced peritoneal inflammation [26].

6. Conclusions

Here, we summarize the *in vivo* effects of Tyk2-mediated signaling on immune and inflammatory responses. Tyk2 mediates signals for the constitutive production of type I IFNs to rapidly respond against invading pathogens as well as for the promotion and activation of Th1 and/or Th17 cells to induce appropriate immune and inflammatory responses [8–10,12]. In addition, as described here, Tyk2-mediated signaling suppresses the *in vivo* production of IL-10, a strong immune-inhibitory cytokine [26]. Although molecular mechanisms how Tyk2-deficiency induces high IL-10 production remains unclear, it is known that the PGE_2-PKA pathway, but not the IFN systems, is regulated by Tyk2-related molecular events. Therefore, Tyk2 is widely involved in multiple cellular events regulating immune and/or inflammatory responses.

In several murine experimental autoimmune model studies, Tyk2-deficient mice show less immune/inflammatory phenotypes, as described above [6,12,19]. However, in the case of virus-induced diabetes model, loss of Tyk2 expression by naturally occurring Tyk2 gene mutation enhances encephalomyocarditis strain D virus infection, leading to severe islet damages [28]. In addition, TYK2 polymorphism variants are enriched in the subgroup of insulin-dependent Japanese patients via increasing susceptibility to infection as well as diabetes [29,30].

Tyk2 selective inhibitor, deucravacitinib (BMS-986165), are tested in a clinical phase II trial, which targets at patients with psoriasis, and the response rate was significantly higher in the deucravacitinib group than in the placebo group [31]. Therefore, Tyk2 inhibitors have a potential to provide a better strategy of treatment for patients with immune/inflammatory diseases compared to the currently marketed biologics.

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Conflict of interest

All authors declare no conflicts of interest in this paper.

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