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MINIREVIEWS

Current understanding of the role of tyrosine kinase 2 signaling in immune responses

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Abstract

Immune system is a complex network that clears pathogens, toxic substrates, and cancer cells. Distinguishing self-antigens from non-self-antigens is critical for the immune cell-mediated response against foreign antigens. The innate immune system elicits an early-phase response to various stimuli, whereas the adaptive immune response is tailored to previously encountered antigens. During immune responses, B cells differentiate into antibody-secreting cells, while naïve T cells differentiate into functionally specific effector cells [T helper 1 (Th1), Th2, Th17, and regulatory T cells]. However, enhanced or prolonged immune responses can result in autoimmune disorders, which are characterized by lymphocyte-mediated immune responses against self-antigens. Signal transduction of cytokines, which regulate the inflammatory cascades, is dependent on the members of the Janus family of protein kinases. Tyrosine kinase 2 (Tyk2) is associated with receptor subunits of immune-related cytokines, such as type I interferon, interleukin (IL)-6, IL-10, IL-12, and IL-23. Clinical studies on the therapeutic effects and the underlying mechanisms of Tyk2 inhibitors in autoimmune or chronic inflammatory diseases are currently ongoing. This review summarizes the findings of studies examining the role of Tyk2 in immune and/or inflammatory responses using *Tyk2*-deficient cells and mice.

Key Words: Tyrosine kinase 2; Cytokines; Signal transduction; Immune system; Inflammation

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Core Tip: Studies on murine *tyrosine kinase 2 (Tyk2)*-deficient models were reviewed to examine the role of Tyk2 dysregulation in human diseases. *Tyk2*-deficient mice exhibit reduced responses in several interleukin-12 (IL-12)/Th1- and IL-23/Th17-mediated models of diseases, including rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases, psoriasis, sarcoidosis, and delayed-type hypersensitivity. These findings demonstrate a broad contribution of Tyk2 to immune responses. Tyk2 represents a candidate for drug development by targeting both the IL-12/Th1 and IL-23/Th17 axes.

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INTRODUCTION

Cytokines function as effectors and regulate the proliferation, differentiation, and functions of immune cells and consequently aid in the clearance of invading pathogens. However, cytokines are also involved in the onset and development of autoimmune diseases[1]. Cytokine-specific cell surface receptors exhibit conformational changes upon activation, which result in activation of the Janus family of protein tyrosine kinases (Jaks). Activated Jaks promote the recruitment and phosphorylation of the transcription factor signal transducer and activator of transcription (STAT). Nuclear translocation of activated STATs induces the expression of cytokine-responsive genes. Thus, the Jak-STAT pathway transduces signals from various cytokine receptor superfamily members[2-4].

The Jak family comprises Jak1, Jak2, Jak3, and tyrosine kinase 2 (Tyk2), which are activated by distinct cytokines[2-4]. Jak1 binds to interferon (IFN), interleukin (IL)-6, and IL-10 receptors that contain a common γ chain and gp130 subunit, while Jak2 binds to IL-3 and erythropoietin, growth hormone, and prolactin hormone-like receptors. Tyk2 binds to IFN, IL-12, and IL-23 receptors. Jak3, whose expression is localized to hematopoietic cells, binds exclusively to receptors that contain common γ chains along with Jak1. Moreover, *Jak1* deficiency in mice results in perinatal lethality and impaired lymphocyte development[5]. The embryonic lethality in *Jak2*-deficient mice is attributed to insufficient definitive erythropoiesis[6]. *Jak3* deficiency results in dysfunctional mature T and B lymphocytes and leads to severe combined immunodeficiency[7,8]. Although *Tyk2*-deficient mice are viable, they are susceptible to viral infections[9,10].

Previous studies using experimental models, such as *Tyk2*-deficient mice have demonstrated that Tyk2 primarily functions in the IL-12 and IFN-α/β signaling pathways[9,10]. In humans, a mutation in *TYK2*, which causes an autosomal recessive form of hyper IgE syndrome (AR-HIES), affects the IL-23, IL-10, and IL-6 signal transduction pathways (Figure 1)[11]. Tyk2 is involved in both innate and acquired immunity. Here, the current knowledge on the involvement of Tyk2 in immune responses has been reviewed, and the potential clinical applications of Tyk2 inhibitors have been discussed.

ROLE OF TYK2 IN INFLAMMATORY RESPONSES

IFN system

Tyk2 was originally identified as a protein kinase that can compensate for the loss of IFN response in mutant fibroblasts[12]. IFN-α specifically activates Tyk2 and Jak1, which leads to the phosphorylation of STAT1 and STAT2 and the dimerization of activated STATs. The nuclear translocation of dimerized STATs induces the expression of target genes[3,13].

Type I IFNs are constitutively expressed in various cells, including macrophages. Although the constitutive expression of type I IFNs is low, they can regulate physiological cellular functions in an autocrine or a paracrine manner[14,15]. Tyk2

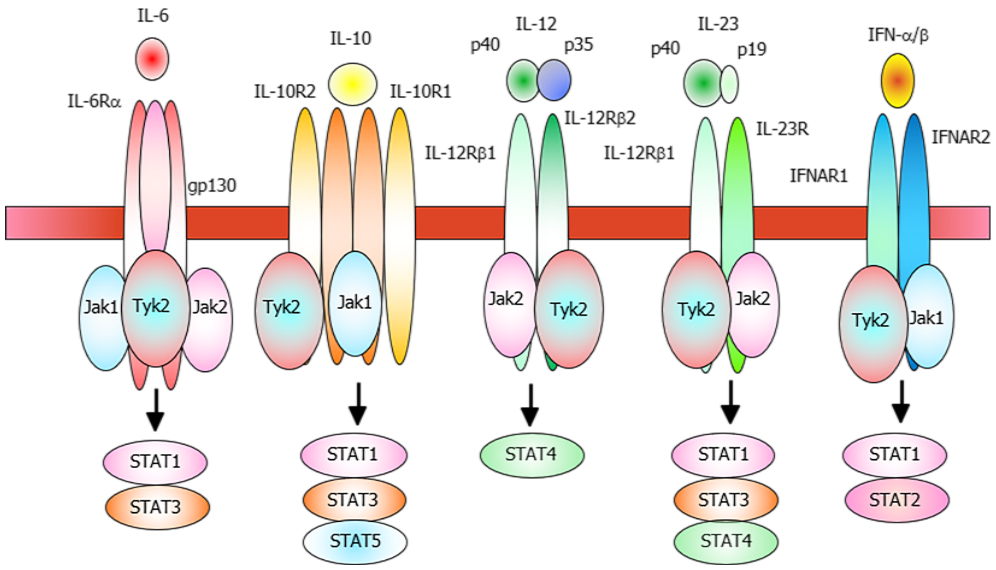

Figure 1 Schematic representation of the tyrosine kinase 2-related cytokine receptors. The IL-6 receptor, which comprises IL6RA (gp80) and IL6RB (gp130) subunits, activates signal transducer and activator of transcription (STAT)1 and STAT3 through interactions with Tyrosine kinase 2 (Tyk2), Janus family of protein tyrosine kinases 1 (Jak1), and Jak2. The IL-10 receptor, which comprises IL-10R1 and IL10-R2 subunits, activates STAT1, STAT3, and STAT5 through interactions with Tyk2 and Jak1. IL-12 is a heterodimeric cytokine comprising the IL-12p35 and IL-12p40 subunits. The IL-12 receptor, which comprises IL-12Rβ1 and IL-12Rβ2, mainly activates STAT4 through interactions with Tyk2 and Jak2. The IL-12p40 component of IL-23 can dimerize with IL-23p19 to form IL-23. The IL-23 receptor, which comprises IL-12Rβ1 and IL-23R subunits, activates STAT1, STAT3, and STAT4 through interactions with Tyk2 and Jak2. The type I IFN receptor, which comprises IFNAR1 and IFNAR2 subunits, activates STAT1 and STAT2 through interactions with Tyk2 and Jak1. STAT: Signal transducer and activator of transcription; Tyk2: Tyrosine kinase 2; Jak1: Janus family of protein tyrosine kinases 1.

promotes the constitutive production of type I IFNs in macrophages under steady-state conditions, as well as during the innate immune responses against bacterial components. The basal and lipopolysaccharide (LPS)-induced expression levels of type I IFN are dysregulated in *Tyk2*-deficient macrophages[16]. Moreover, *Tyk2*-deficient and *Ifnb*-deficient mice are resistant to high-dose LPS-induced lethal septic shock[16, 17]. Additionally, the expression of type I IFN-responsive genes, especially under steady-state conditions, was downregulated in *Tyk2*-deficient macrophages[18]. Therefore, Tyk2 is partially involved in macrophage activation by regulating autocrine and/or exogenous IFN production in the neighboring immune cells.

IL-12 and IL-23 systems

Helper T cells can be classified into the following two subsets based on their cytokine profiles: T helper 1 (Th1) and Th2 cells[19]. IL-12 and IL-4 promote the differentiation of naïve CD4$^+$ T cells into Th1 cells and Th2 cells, respectively. Heterodimeric IL-12 comprises covalently linked p35 and p40 subunits. Both IL-12 and IL-23 comprise the p40 subunit[20]. IL-23 (comprising p40 and unique p19 subunits) promotes the differentiation of Th17 cells, which secrete the effector cytokines IL-17, IL-21, and IL-22[21, 22]. Th17 cells can promote enhanced inflammatory responses to eliminate microbial pathogens. However, Th17 cells are considered highly pathogenic as excessive and prolonged activation of Th17 cells can result in autoimmune and inflammatory disorders, including inflammatory bowel diseases (IBD) and rheumatoid arthritis (RA), in humans (Figure 2)[21,22].

The activation of IL-12 receptor, which is associated with Tyk2 and Jak2, activates STAT4[23,24]. Phosphorylated Stat4 along with signals from the activated T cell receptor induces the expression of T-bet, which is a master transcriptional factor for Th1 differentiation[25]. IL-23, whose receptor is associated with Tyk2, induces the proliferation, survival, and functional maturation of Th17 cells[22,26] although Th17 cell differentiation is dependent on signals from TGF-β and IL-6 (Figure 3)[22]. STAT3, a major downstream effector of the Th17-related cytokine pathway, is critical for commitment to the Th17 Lineage, whereas STAT4 and STAT6 are essential for commitment to the Th1 and Th2 Lineages, respectively[27,28]. Additionally, *Tyk2*-deficient macrophages do not produce nitric oxide in response to LPS stimulation[16]. *Tyk2*-deficient dendritic cells do not produce IL-12 and IL-23 upon stimulation with CpG oligodeoxynucleotides and consequently cannot induce Th1 cell differentiation

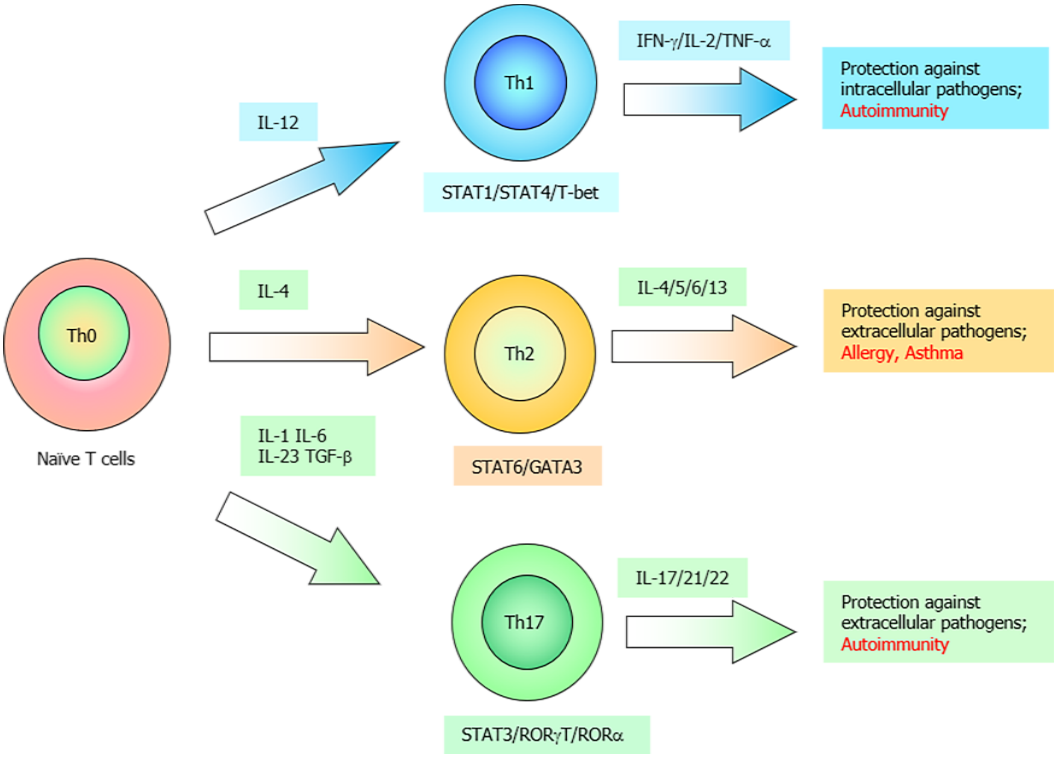

Figure 2 Schematic representation of naïve T cell differentiation into T helper 1, T helper 2, or T helper 17 cells depending on the cytokine profile. IL-12 promotes the differentiation of naïve T cells into Th1 cells. Th1 cells promote the clearance of intracellular pathogens and induce autoimmunity through the production of IFN-γ, IL-2, and TNF-α. Th1 differentiation is regulated by transcription factors such as signal transducer and activator of transcription (STAT)1, STAT4, and T-bet. IL-4 promotes the differentiation of naïve T cells into Th2 cells. Th2 cells promote the clearance of extracellular pathogens and induce allergic responses through the production of IL-4, IL-5, IL-6, and IL-13. Th2 differentiation is regulated by transcription factors such as STAT6 and GATA3. TGF-β, IL-6, and IL1 promote the differentiation of naïve T cells into Th17 cells, while IL-23 can maintain the Th17 phenotype. Th17 cells promote the clearance of extracellular pathogens and induce autoimmunity through the production of IL-17, IL-21, and IL-22. Th2 differentiation is regulated by transcription factors, such as STAT3, RORγt and RORα.

[29]. Therefore, Tyk2 is involved in the host defense response by regulating the production and function of both Th1 and Th17 cells.

Inhibitory effects of type I IFNs on B lymphopoiesis are mediated through the TYK2-DAXX axis

Interactions between IFN-α and its receptor promote potent antiviral and antiproliferative activities against the target cells[3,4]. IFN-α stimulation specifically activates Tyk2 and Jak1, which leads to the phosphorylation of STAT1 and STAT2. Nuclear translocation of phosphorylated STATs (in the form of homodimers or heterodimers) promotes target gene expression[3,4]. *Jak1*-deficient cells are not responsive to IFN-α stimulation[30], whereas *Tyk2*-deficient cells cannot inhibit lymphocyte growth[31]. Additionally, *Stat1*-deficient mice do not respond to IFN-α simulation[32,33], while *Stat2*-deficient mice are highly susceptible to viral infections[34].

Analysis of the colony forming unit (CFU) of bone marrow cells in the presence of IL-7 is a powerful tool to evaluate the growth capacity of B lymphocyte progenitors [35]. The CFU values of bone marrow cells in the presence of IL-7 were not markedly different between wild-type (WT) and *Tyk2*-deficient mice, which indicated that Tyk2 did not affect the number of IL-7-responsive B lymphocyte progenitors under steady-state conditions[31]. IFN-α, which is a potent inhibitor of IL-7-dependent growth of B lymphocyte progenitors, effectively inhibits B lymphocyte differentiation at the pro-B cell stage[36]. The CFU values of WT bone marrow cells in the presence of IL-7 markedly decreased upon stimulation with IFN-α. In contrast, the CFU values of *Tyk2*-deficient bone marrow cells in the presence of IL-7 did not decrease upon stimulation with IFN-α[31]. The knockout of *Tyk2* completely inhibited the IFN-α -induced elevation and nuclear accumulation of death-associated protein (Daxx)[31]. Daxx was originally identified as a Fas-binding protein[37] and it plays crucial roles in the type I IFN-induced growth suppression of B lymphocyte progenitors[38]. One study used the

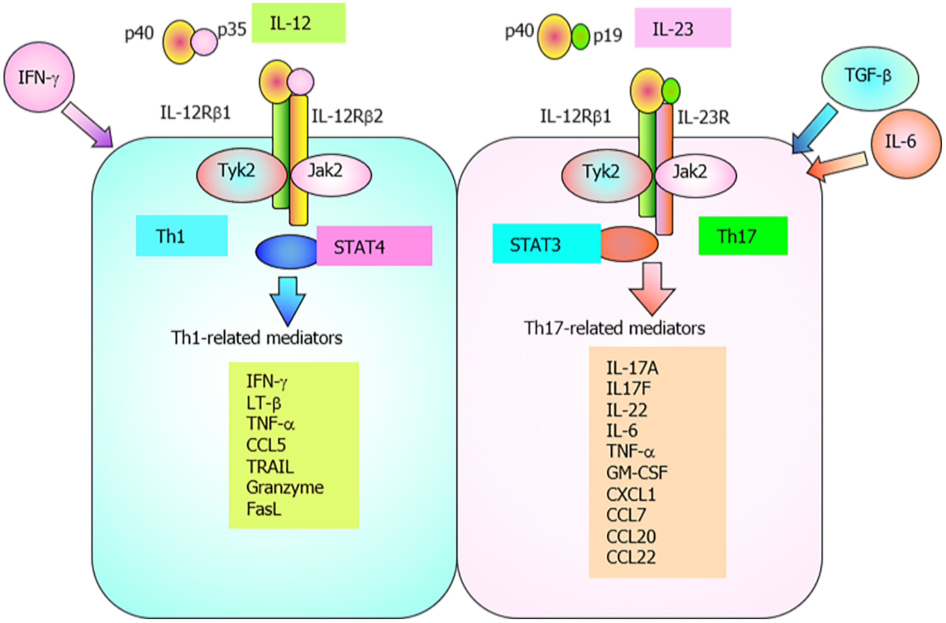

Figure 3 Illustration of interleukin-12 and interleukin-23, as well as their receptors and downstream signaling pathways. IL-12 and IL-23 share the p40 subunit, while their receptors share the IL-12Rβ1 subunit. The binding of IL-12 to its receptor induces the activation of Jak2 and Tyrosine kinase 2 (Tyk2), which results in signal transducer and activator of transcription (STAT)4 phosphorylation. Activated STAT4 promotes the differentiation of naïve Th cells into Th1 cells, which subsequently produce IFN-γ that is required for the development of Th1 immune response. The binding of IL-23 to its receptor induces the activation of Jak2 and Tyk2, which results in STAT3 phosphorylation. IL-23 induces the expression of IL-17A, IL-17F, and/or IL-22 and stabilizes Th17 cells. STAT: Signal transducer and activator of transcription.

sumoylation-defective Daxx KA mutant (Daxx K630/631A) to investigate the involvement of Daxx in decreasing the growth of Ba/F3 pro-B cells in the presence of IL-7 through IFN-α. The study demonstrated that Daxx KA is localized to the cytoplasm, whereas Daxx WT is localized to the nucleus[39]. Moreover, overexpression of Daxx KA conferred resistance to IFN-α -induced growth inhibition in a murine pro-B cell line Ba/F3. Treating Daxx KA-expressing Ba/F3 cells with leptomycin B, an exportin inhibitor, enhanced the nuclear localization of Daxx KA, and the growth of the cells was suppressed upon stimulation with IFN-α. Additionally, Daxx KA binds only weakly to promyelocytic leukemia protein (PML), which aids in the nuclear localization of Daxx. Conversely, overexpression of PML promotes the recruitment of Daxx to the PML nuclear bodies. A fusion protein comprising Daxx and a small ubiquitin-related modifier enhances the nuclear localization of Daxx and inhibits Ba/F3 cell growth. This indicates that IFN-α -induced inhibition of B lymphocyte progenitor growth requires nuclear localization of Daxx, which is dependent on sumoylation and interactions with PML. Therefore, the Tyk2-Daxx axis plays an essential role in IFN-α -induced growth inhibition of B lymphocyte progenitors.

PATHOLOGICAL SIGNIFICANCE OF TYK2 IN IMMUNE AND INFLAMMATORY DISEASES: DATA FROM MURINE EXPERIMENTAL MODELS

RA

RA is associated with joint inflammation and pain owing to a runaway immune system that elicits immune responses against the synovium of the joints of the hands, knees, or ankles. Murine experimental models for arthritis have provided useful information on various cellular and molecular mechanisms associated with RA[40].

Collagen-induced arthritis (CIA) mice are widely utilized as an experimental model for human RA[41]. Development of arthritis involves the production of autoantibodies in response to collagen and the subsequent inflammatory response against joints. Mice harboring *Tyk2* polymorphisms exhibit differential susceptibility to CIA[42,43]. B10.Q/Ai mice are highly susceptible to CIA, whereas B10.D1 mice are resistant. This suggests that *Tyk2* deficiency results in the defined clinical RA.

Monitoring of the inflammatory response in the anti-type II collagen (CII) antibody-induced arthritis (CAIA) experimental model provides useful information on the mechanisms of RA[44]. *Tyk2*-deficient mice are highly resistant to the development of CAIA. Histological analysis has revealed that *Tyk2* deficiency downregulated the inflammatory cell infiltration into the synovium[45]. Additionally, the production of IFN-γ, tumor necrosis factor (TNF)-α, IL-6, and matrix metalloproteinases (MMPs) was severely impaired in *Tyk2*-deficient mice[45]. TNF-α and IL-6, which are secreted by macrophages, function as pro-inflammatory cytokines in the CAIA model. MMPs, which are expressed in chondrocytes, synoviocytes, and macrophages, are reported to be involved in the degradation and damage of articular cartilage[46,47]. *Tyk2*-deficient macrophages cannot produce nitric oxide in response to LPS stimulation. Meanwhile, *Tyk2*-deficient dendritic cells cannot produce IL-12 and IL-23 in response to CpG oligodeoxynucleotides[29]. The potential mechanisms were analyzed using the anti-CII monoclonal antibody, which induced the phosphorylation of STAT3 and STAT4 in the draining lymph node cells. Phosphorylated STAT3 and STAT4 were detected in WT but not in *Tyk2*-deficient mice[45]. This suggests that Tyk2 promotes the production and downstream signaling of Th1/Th17-related cytokines, which are activated through STAT3 and STAT4.

Tyk2 deficiency markedly decreased the susceptibility to arthritis development in both CIA and CAIA murine models, which indicated that Tyk2 plays an important role in adaptive autoimmunity and inflammatory responses. Therefore, Tyk2 regulates multiple steps involved in the onset and development of RA.

Multiple sclerosis

Multiple sclerosis (MS) is characterized by the lack of myelin, a protective sheath covering nerve fibers, which leads to disruption of the communication between the brain and other tissues[48]. Patients with MS exhibit various symptoms, such as difficulty in walking and balancing, muscle weakness and spasticity, and loss of concentration and memory. The murine experimental autoimmune encephalomyelitis (EAE) model, which is an animal model for human MS, is triggered by immunization with myelin antigens or by the adoptive transfer of myelin-specific CD4$^+$ effector cells [49]. *Tyk2*-deficient mice exhibit decreased clinical scores and limited lymphocyte infiltration into the inflamed central nervous system[50]. The involvement of Tyk2 in EAE was confirmed using mice harboring different *Tyk2* polymorphisms. B10.D1 mice, which harbor the *Tyk2A* allele, are resistant to EAE development. The insufficient responses can be compensated by one copy of the *Tyk2G* allele from B10.Q/Ai mice [51].

IBD

Crohn's disease is characterized by inflammation of the digestive tract. Patients with Crohn’s disease exhibit severe diarrhea, abdominal pain, fatigue, weight loss, and malnutrition[52]. Dextran sulfate sodium (DSS)-induced colitis, a mouse model for human Crohn’s disease, is generated by supplementing mice with DSS through drinking water. The disease activity index and histological score were assessed using the combined scores of weight loss, consistency, and bleeding and acute clinical symptoms with diarrhea and/or extremely bloody stools[53]. Compared with that in WT DSS-induced colitis mice, disease development was delayed in *Tyk2*-deficient DSS-induced colitis mice[45]. Oral supplementation of DSS activates intestinal macrophages, which leads to enhanced production of inflammatory cytokines and chemokines. Subsequently, lymphocytes are recruited to the inflammatory sites and elicit Th1 and/or Th17 responses. During this inflammatory process, Tyk2 can regulate the functions of macrophages and dendritic cells, as well as the Th1 and Th17 responses. Indeed, the mRNA levels of DSS-induced Th1 cell-related or Th17 cell-related cytokines were significantly downregulated in the colon tissues of *Tyk2*-deficient mice [45]. A genome-wide association study identified *Tyk2* as a Crohn’s disease susceptibility locus[54].

Ulcerative colitis is characterized by inflammation and ulcers in the large intestine and rectum. Patients with ulcerative colitis exhibit diarrhea with bloody stool, abdominal pain, fever, and body weight loss[55]. To model human ulcerative colitis in mice, 2,4,6-trinitrobenzene sulfonic acid (TNBS) is used[45]. WT mice treated with TNBS die within 3 days due to the induction of massive colitis. However, approximately 50% of *Tyk2*-deficient mice survive after treatment with TNBS. Additionally, the bodyweight of the surviving mice returned to the physiological range after recovery from diarrhea[45].

Therefore, Tyk2 is a key molecule for the development of IBD.

Psoriasis

Psoriasis is characterized by scaly erythematous lesions in the skin, epidermal hyperplasia, parakeratosis, and accumulation of inflammatory cells[56]. The inflammatory response is mediated by several cytokines, such as TNF-α, IL-17, and IL-23. The mouse model for human psoriasis was developed by treatment with imiquimod (IMQ), a ligand for TLR7[57]. *Il23p19*-deficient and *Il17a*–deficient mice exhibit decreased scores for erythema, scaling, and thickness upon treatment with IMQ, which suggests that the IL-23/Th17 axis and the Th17 cell-produced cytokines are essential for the development of skin abnormalities[57]. A genome-wide association study identified *Tyk2* as a psoriasis susceptibility locus[54]. *Tyk2* deficiency mitigates IMQ-induced enhanced ear thickness, which results from epidermal hyperplasia and inflammatory cell infiltration[45]. *Tyk2*-deficient mice exhibit markedly decreased numbers of $CD4^+IL\text{-}17^+$ or $CD4^+IFN\text{-}\gamma^+$ T cells in the draining lymph nodes and downregulated mRNA levels of Th17 cell-related cytokines upon treatment with IMQ [45].

The IL-23-induced skin inflammation mouse model is another promising model for human psoriasis[58]. In this IL-23-induced model, *Tyk2*-deficient mice exhibited reduced ear skin swelling, epidermal hyperplasia, Th17 and IL-22-producing Th22 cell infiltration compared with wild-type mice[45]. *Tyk2* deficiency downregulates the production of pro-inflammatory cytokines and psoriasis-related anti-microbial peptides.

IL-23 and IL-22 coordinate to promote skin inflammation[58,59]. Tyk2-mediated signals are essential for the induction of enhanced leukocyte infiltration and inflammatory cytokine production. Enhanced keratinocyte proliferation and differentiation are highly dependent on IL-17 and IL-22. Previous studies have reported that Tyk2 directly regulates IL-22-dependent processes as evidenced by the downregulation of STAT3 phosphorylation in *Tyk2* knockdown human keratinocyte HaCaT cells after IL-22 stimulation[45]. Therefore, Tyk2 has a critical role in the IL-22 signaling cascade that is involved in inducing epidermal hyperplasia.

IκB-ζ, an IL-17-induced protein encoded by *NFKBIZ*[60], is upregulated in the epidermal keratinocytes of psoriatic lesions[61]. *NFKBIZ* is located in the psoriasis susceptibility locus at 3q12.3[62]. IκB-ζ, a nuclear IκB family protein, positively or negatively modulates NF-κB-dependent and/or STAT3-dependent transcription[63-65]. Tyk2 is involved in IL-17–induced IκB-ζ expression in keratinocytes[66]. *Tyk2*-deficient mice exhibited only slight inflammation and downregulated mRNA levels of *Nfkbiz* upon treatment with IMQ. The catalytic activities of Tyk2 and STAT3 are required for IκB-ζ promoter activity in the HaCaT cells. The signaling pathways activated by IL-17 regulate mRNA stability[66-70]. ZC3H12A, which exhibits endoribonuclease activity, functions as a negative feedback regulator for inflammatory signaling[71-74]. The ubiquitin-proteasome pathway rapidly degrades ZC3H12A in IL-17-treated, IL-1β-treated, or IL-36–treated keratinocytes[72,74], which suggests that the stimulus-induced ZC3H12A downregulation can markedly suppress the inhibitory effects on mRNA expression.

Therefore, Tyk2 promotes the development of psoriasis by transducing IL-22 and IL-23 signals and regulating NFKBIZ along with the IL-17/ZC3H12A axis.

Sarcoidosis

Sarcoidosis is characterized by the aberrant accumulation of inflammatory cells, which typically form granulomas. Sarcoidosis usually begins in the lungs, skin, lymph nodes, eyes, heart, or other organs[75]. The murine model for human sarcoidosis is developed by intraperitoneally administering mice with heat-killed *Propionibacterium acnes* (*P. acnes*), which induces dense granulomas in the liver[76]. IL-12-IFN-γ axis is required for the induction since neither *Ifngr*-deficient nor *Il12p40*-deficient mice form hepatic granulomas after *P. acnes* injection[76]. *Tyk2*-deficient mice injected with *P. acnes* exhibit reduced serum IFN-γ level and decreased formation of hepatic granulomas compared with wild-type mice[45], indicating that Tyk2 has a role in *P. acnes*-induced granuloma formation.

Delayed-type hypersensitivity

Delayed-type hypersensitivity (DTH), which protects against various pathogens, such as mycobacteria, fungi, and parasites, contributes to transplant rejection and tumor immunity[77]. DTH is mainly dependent on T cells and develops 24–72 h after exposure to a foreign antigen. The DTH response analysis is based on a Th1/Th17 type model as the hypersensitivity response is defective in *Il12p40*-deficient and *Il23p19*-

deficient mice[78]. The sensitization phase is triggered by immunizing mice with a specific protein antigen (methylated BSA). The elicitation phase, which is initiated by the second injection of methylated BSA into the rear footpad of the pre-immunized mice, results in footpad swelling. Footpad swelling was significantly alleviated in *Tyk2* -deficient mice, which indicated the role of Tyk2 in DTH responses[45].

HIES

Tyk2 AR-HIES is a hereditary (autosomal recessive) disease involving a *Tyk2* mutation [79]. Patients with Tyk2 AR-HIES are characterized by repeated viral and mycobacterial infections, atopic dermatitis, and enhanced levels of IgE[11]. Therefore, Tyk2 may have a broader and more important role in immunological responses than expected from studies conducted using *Tyk2*-deficient mice.

POTENTIAL CLINICAL APPLICATIONS OF TYK2 INHIBITORS

The first *in vivo* evidence for the roles of Jaks in cytokine signaling originated from a human case study of severe combined immunodeficiency. Mutations in Jak3 or its receptor (a common g cytokine receptor chain) were detected in this case[80,81]. Another example is a somatic Jak2 valine-to-phenylalanine mutation (V617F), which is detected in more than 90% of the patients with polycythemia and some patients with essential thrombocythemia and primary myelofibrosis[82]. Activating point mutations in *Jak1* are detected in DNA samples from patients with acute lymphoblastic leukemia and are rarely observed in patients with acute myeloid leukemia[83]. Thus, dysregulation of the Jak-mediated signaling pathway is associated with the pathogenesis of different diseases, including hematological malignancies, autoimmune diseases, and immune-disrupted conditions. Studies on *Tyk2*-deficient mice or human patients with mutated *Tyk2* alleles have revealed that Tyk2 is a key player in the pathogenesis of autoimmune and/or inflammatory diseases.

Imatinib, a Bcr-Abl kinase inhibitor, exerts potent therapeutic effects in patients with chronic myelocytic leukemia[84]. Hence, various kinase inhibitors with strict selectivity and potency have been developed[85]. Jak inhibitors exert potent therapeutic effects by mitigating high levels of circulating immune/inflammatory cytokines. These results strongly suggest that Tyk2 is a potential therapeutic target for patients with immune and/or inflammatory diseases.

First-generation Jak inhibitors typically target two or three Jak types. Therefore, first-generation Jak inhibitors are associated with broader effects and more adverse events than the new-generation drugs, which specifically target one Jak type. Currently, several Jak inhibitors are used to treat various human diseases[86]. For example, ruxolitinib, an inhibitor of Jak1 and Jak2, has been approved to treat patients with myelofibrosis and polycythemia vera[87]. Tofacitinib, an inhibitor of Jak1, Jak2, and Jak3, has been approved to treat patients with RA, psoriatic arthritis, and ulcerative colitis[88]. Baricitinib, an inhibitor of Jak1 and Jak2, is used to treat patients with RA[89]. In methotrexate-inadequate responders, both tofacitinib and baricitinib provided enhanced therapeutic responses in patients with RA when compared with placebo[90]. In a phase 2 trial involving patients with psoriasis, the response rate to deucravacitinib (BMS-986165), a Tyk2 selective inhibitor[91], was significantly higher than that to placebo after 12 wk of administration. Treatment with BMS-986165 did not affect the blood cell counts or the serum levels of liver enzymes, lipids, and creatinine. However, BMS-986165 was associated with some severe adverse effects, such as malignant melanoma. Theoretically, therapeutic strategies targeting the immune system may increase the risk of infections from various pathogens, such as herpes zoster virus, cytomegalovirus, and Epstein–Barr virus. Therefore, further studies are needed to determine the long-term efficacy and safety of Tyk2 inhibitors. Additionally, clinical trials on Tyk2 inhibitors will aid in devising better therapeutic strategies for immune/inflammatory diseases than the currently marketed therapeutics.

CONCLUSION

This review summarized the involvement of Tyk2 in the immune system and its possible potential roles in the onset and development of immune and inflammatory diseases (Figure 4).

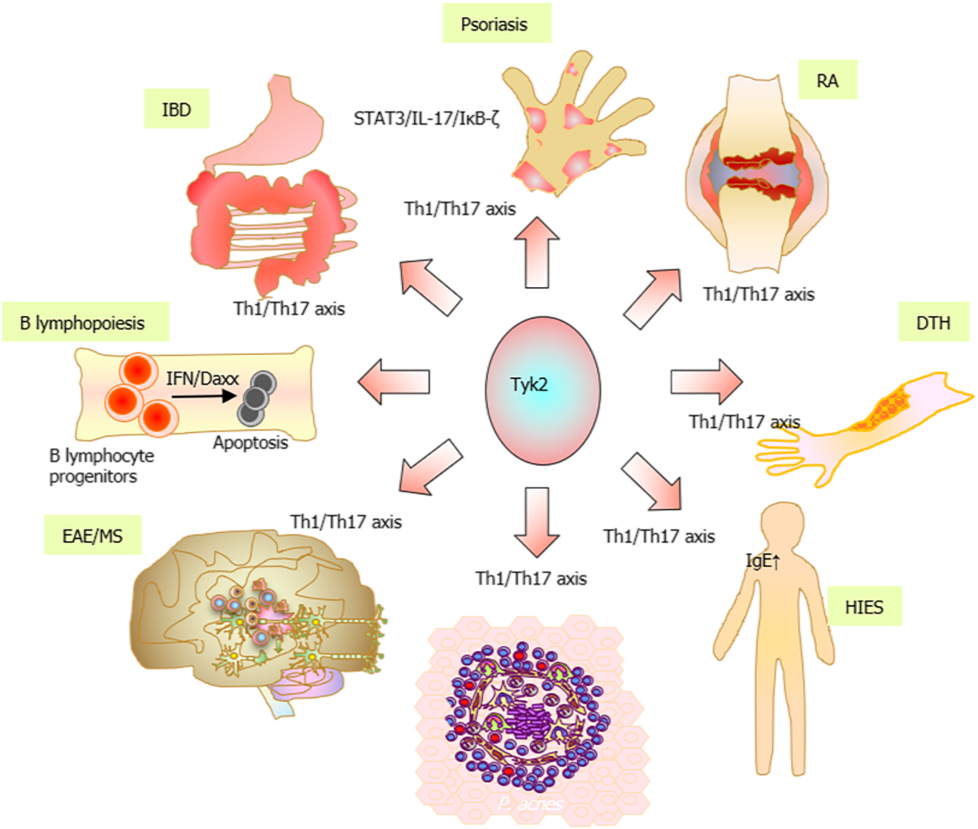

Figure 4 Schematic representation of the involvement of tyrosine kinase 2 in immune and inflammatory responses and its pathological significance. IBD: Inflammatory bowel diseases; RA: Rheumatoid arthritis; DTH: Delayed-type hypersensitivity; HIES: Hyper IgE syndrome; EAE: Experimental autoimmune encephalomyelitis; MS: Multiple sclerosis.

Studies on the *Tyk2*-deficient cells have revealed the involvement of the IFN system and IL-12/IL-23 axis. Constitutive production of a small amount of type I IFNs elicits a pro-inflammatory response against the invading pathogens and mitigates aberrant inflammation by promoting the expression of IL-10, a potent anti-inflammatory cytokine. Tyk2 is critical for maintaining the basal levels of IFNs. The IFN-α-induced decreased CFUs of bone marrow cells in the presence of IL-7 were also dependent on Tyk2. Tyk2 contributes to IFN-α signaling by promoting the nuclear translocation of Daxx and the formation of the Daxx/PML complex, which leads to growth inhibition. Additionally, Tyk2 interacts with the receptors for type I IFN, IL-6, IL-10, IL-12, and IL-23 (Figure 1). Moreover, Tyk2 is essential for IL-12-induced differentiation into Th1 cells, as well as IL-23-induced proliferation, survival, and functional maturation of Th17 cells. Additionally, Tyk2 mediates the production of nitric oxide in macrophages and IL-12 and IL-23 in dendritic cells after the invasion of pathogens.

Studies using *Tyk2*-deficient mice have revealed the potential involvement of Tyk2 in the onset and development of various immune and/or inflammatory disorders, such as RA, MS, IBD, psoriasis, sarcoidosis, and DTH. The development of most phenotypes in these models was mediated by Th1 and Th17 cells, whose differentiation and functions are highly dependent on Tyk2. Additionally, Tyk2 contributes to IL-17-induced IκB-ζ expression in IMQ-induced skin inflammation.

The experimental data summarized in this review along with the known clinical success of the novel Jak inhibitors indicate the therapeutic potential of Tyk2 inhibitors in the clinical setting. Further clinical trials are needed to examine the safety and efficacy profiles of Tyk2 inhibitors for treating psoriasis. Additionally, Tyk2 inhibitors are likely to be widely approved for various Th1/Th17-related immune/inflammatory diseases.

REFERENCES

1 **O'Shea JJ**, Ma A, Lipsky P. Cytokines and autoimmunity. *Nat Rev Immunol* 2002; **2**: 37-45 [PMID: 11905836 DOI: 10.1038/nri702]

2 **Ihle JN**. Cytokine receptor signalling. *Nature* 1995; **377**: 591-594 [PMID: 7566171 DOI: 10.1038/377591a0]

3 **Darnell JE**. STATs and gene regulation. *Science* 1997; **277**: 1630-1635 [PMID: 9287210 DOI: 10.1126/science.277.5332.1630]

4 **Stark GR**, Darnell JE Jr. The JAK-STAT pathway at twenty. *Immunity* 2012; **36**: 503-514 [PMID: 22520844 DOI: 10.1016/j.immuni.2012.03.013]

5 **Rodig SJ**, Meraz MA, White JM, Lampe PA, Riley JK, Arthur CD, King KL, Sheehan KC, Yin L, Pennica D, Johnson EM Jr, Schreiber RD. Disruption of the Jak1 gene demonstrates obligatory and nonredundant roles of the Jaks in cytokine-induced biologic responses. *Cell* 1998; **93**: 373-383 [PMID: 9590172 DOI: 10.1016/s0092-8674(00)81166-6]

6 **Parganas E**, Wang D, Stravopodis D, Topham DJ, Marine JC, Teglund S, Vanin EF, Bodner S, Colamonici OR, van Deursen JM, Grosveld G, Ihle JN. Jak2 is essential for signaling through a variety of cytokine receptors. *Cell* 1998; **93**: 385-395 [PMID: 9590173 DOI: 10.1016/s0092-8674(00)81167-8]

7 **Nosaka T**, van Deursen JM, Tripp RA, Thierfelder WE, Witthuhn BA, McMickle AP, Doherty PC, Grosveld GC, Ihle JN. Defective lymphoid development in mice lacking Jak3. *Science* 1995; **270**: 800-802 [PMID: 7481769 DOI: 10.1126/science.270.5237.800]

8 **Macchi P**, Villa A, Giliani S, Sacco MG, Frattini A, Porta F, Ugazio AG, Johnston JA, Candotti F, O'Shea JJ. Mutations of Jak-3 gene in patients with autosomal severe combined immune deficiency (SCID). *Nature* 1995; **377**: 65-68 [PMID: 7659163 DOI: 10.1038/377065a0]

9 **Shimoda K**, Kato K, Aoki K, Matsuda T, Miyamoto A, Shibamori M, Yamashita M, Numata A, Takase K, Kobayashi S, Shibata S, Asano Y, Gondo H, Sekiguchi K, Nakayama K, Nakayama T, Okamura T, Okamura S, Niho Y. Tyk2 plays a restricted role in IFN alpha signaling, although it is required for IL-12-mediated T cell function. *Immunity* 2000; **13**: 561-571 [PMID: 11070174 DOI: 10.1016/s1074-7613(00)00055-8]

10 **Karaghiosoff M**, Neubauer H, Lassnig C, Kovarik P, Schindler H, Pircher H, McCoy B, Bogdan C, Decker T, Brem G, Pfeffer K, Müller M. Partial impairment of cytokine responses in Tyk2-deficient mice. *Immunity* 2000; **13**: 549-560 [PMID: 11070173 DOI: 10.1016/s1074-7613(00)00054-6]

11 **Minegishi Y**, Saito M, Morio T, Watanabe K, Agematsu K, Tsuchiya S, Takada H, Hara T, Kawamura N, Ariga T, Kaneko H, Kondo N, Tsuge I, Yachie A, Sakiyama Y, Iwata T, Bessho F, Ohishi T, Joh K, Imai K, Kogawa K, Shinohara M, Fujieda M, Wakiguchi H, Pasic S, Abinun M, Ochs HD, Renner ED, Jansson A, Belohradsky BH, Metin A, Shimizu N, Mizutani S, Miyawaki T, Nonoyama S, Karasuyama H. Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. *Immunity* 2006; **25**: 745-755 [PMID: 17088085 DOI: 10.1016/j.immuni.2006.09.009]

12 **Velazquez L**, Fellous M, Stark GR, Pellegrini S. A protein tyrosine kinase in the interferon alpha/beta signaling pathway. *Cell* 1992; **70**: 313-322 [PMID: 1386289 DOI: 10.1016/0092-8674(92)90105-l]

13 **Darnell JE Jr**, Kerr IM, Stark GR. Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. *Science* 1994; **264**: 1415-1421 [PMID: 8197455 DOI: 10.1126/science.8197455]

14 **Gough DJ**, Messina NL, Clarke CJ, Johnstone RW, Levy DE. Constitutive type I interferon modulates homeostatic balance through tonic signaling. *Immunity* 2012; **36**: 166-174 [PMID: 22365663 DOI: 10.1016/j.immuni.2012.01.011]

15 **Taniguchi T**, Takaoka A. A weak signal for strong responses: interferon-alpha/beta revisited. *Nat Rev Mol Cell Biol* 2001; **2**: 378-386 [PMID: 11331912 DOI: 10.1038/35073080]

16 **Karaghiosoff M**, Steinborn R, Kovarik P, Kriegshäuser G, Baccarini M, Donabauer B, Reichart U, Kolbe T, Bogdan C, Leanderson T, Levy D, Decker T, Müller M. Central role for type I interferons and Tyk2 in lipopolysaccharide-induced endotoxin shock. *Nat Immunol* 2003; **4**: 471-477 [PMID: 12679810 DOI: 10.1038/ni910]

17 **Kamezaki K**, Shimoda K, Numata A, Matsuda T, Nakayama K, Harada M. The role of Tyk2, Stat1 and Stat4 in LPS-induced endotoxin signals. *Int Immunol* 2004; **16**: 1173-1179 [PMID: 15226272 DOI: 10.1093/intimm/dxh118]

18 **Vogl C**, Flatt T, Fuhrmann B, Hofmann E, Wallner B, Stiefvater R, Kovarik P, Strobl B, Müller M. Transcriptome analysis reveals a major impact of JAK protein tyrosine kinase 2 (Tyk2) on the expression of interferon-responsive and metabolic genes. *BMC Genomics* 2010; **11**: 199 [PMID: 20338026 DOI: 10.1186/1471-2164-11-199]

19 **Mosmann TR**, Coffman RL. TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. *Annu Rev Immunol* 1989; **7**: 145-173 [PMID: 2523712 DOI: 10.1146/annurev.iy.07.040189.001045]

20 **Oppmann B**, Lesley R, Blom B, Timans JC, Xu Y, Hunte B, Vega F, Yu N, Wang J, Singh K, Zonin F, Vaisberg E, Churakova T, Liu M, Gorman D, Wagner J, Zurawski S, Liu Y, Abrams JS, Moore KW, Rennick D, de Waal-Malefyt R, Hannum C, Bazan JF, Kastelein RA. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. *Immunity* 2000; **13**: 715-725 [PMID: 11114383 DOI: 10.1016/s1074-7613(00)00070-4]

21 **Bettelli E**, Korn T, Oukka M, Kuchroo VK. Induction and effector functions of T(H)17 cells. *Nature*

2008; **453**: 1051-1057 [PMID: 18563156 DOI: 10.1038/nature07036]

22 **Korn T**, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 Cells. *Annu Rev Immunol* 2009; **27**: 485-517 [PMID: 19132915 DOI: 10.1146/annurev.immunol.021908.132710]

23 **Bacon CM**, Petricoin EF 3rd, Ortaldo JR, Rees RC, Larner AC, Johnston JA, O'Shea JJ. Interleukin 12 induces tyrosine phosphorylation and activation of STAT4 in human lymphocytes. *Proc Natl Acad Sci U S A* 1995; **92**: 7307-7311 [PMID: 7638186 DOI: 10.1073/pnas.92.16.7307]

24 **Bacon CM**, McVicar DW, Ortaldo JR, Rees RC, O'Shea JJ, Johnston JA. Interleukin 12 (IL-12) induces tyrosine phosphorylation of JAK2 and TYK2: differential use of Janus family tyrosine kinases by IL-2 and IL-12. *J Exp Med* 1995; **181**: 399-404 [PMID: 7528775 DOI: 10.1084/jem.181.1.399]

25 **Robinson DS**, O'Garra A. Further checkpoints in Th1 development. *Immunity* 2002; **16**: 755-758 [PMID: 12121657 DOI: 10.1016/s1074-7613(02)00331-x]

26 **Parham C**, Chirica M, Timans J, Vaisberg E, Travis M, Cheung J, Pflanz S, Zhang R, Singh KP, Vega F, To W, Wagner J, O'Farrell AM, McClanahan T, Zurawski S, Hannum C, Gorman D, Rennick DM, Kastelein RA, de Waal Malefyt R, Moore KW. A receptor for the heterodimeric cytokine IL-23 is composed of IL-12Rbeta1 and a novel cytokine receptor subunit, IL-23R. *J Immunol* 2002; **168**: 5699-5708 [PMID: 12023369 DOI: 10.4049/jimmunol.168.11.5699]

27 **Harris TJ**, Grosso JF, Yen HR, Xin H, Kortylewski M, Albesiano E, Hipkiss EL, Getnet D, Goldberg MV, Maris CH, Housseau F, Yu H, Pardoll DM, Drake CG. Cutting edge: An in vivo requirement for STAT3 signaling in TH17 development and TH17-dependent autoimmunity. *J Immunol* 2007; **179**: 4313-4317 [PMID: 17878325 DOI: 10.4049/jimmunol.179.7.4313]

28 **Wilson CB**, Rowell E, Sekimata M. Epigenetic control of T-helper-cell differentiation. *Nat Rev Immunol* 2009; **9**: 91-105 [PMID: 19151746 DOI: 10.1038/nri2487]

29 **Tokumasa N**, Suto A, Kagami S, Furuta S, Hirose K, Watanabe N, Saito Y, Shimoda K, Iwamoto I, Nakajima H. Expression of Tyk2 in dendritic cells is required for IL-12, IL-23, and IFN-gamma production and the induction of Th1 cell differentiation. *Blood* 2007; **110**: 553-560 [PMID: 17395783 DOI: 10.1182/blood-2006-11-059246]

30 **Müller M**, Briscoe J, Laxton C, Guschin D, Ziemiecki A, Silvennoinen O, Harpur AG, Barbieri G, Witthuhn BA, Schindler C. The protein tyrosine kinase JAK1 complements defects in interferon-alpha/beta and -gamma signal transduction. *Nature* 1993; **366**: 129-135 [PMID: 8232552 DOI: 10.1038/366129a0]

31 **Shimoda K**, Kamesaki K, Numata A, Aoki K, Matsuda T, Oritani K, Tamiya S, Kato K, Takase K, Imamura R, Yamamoto T, Miyamoto T, Nagafuji K, Gondo H, Nagafuchi S, Nakayama K, Harada M. Cutting edge: tyk2 is required for the induction and nuclear translocation of Daxx which regulates IFN-alpha-induced suppression of B lymphocyte formation. *J Immunol* 2002; **169**: 4707-4711 [PMID: 12391177 DOI: 10.4049/jimmunol.169.9.4707]

32 **Meraz MA**, White JM, Sheehan KC, Bach EA, Rodig SJ, Dighe AS, Kaplan DH, Riley JK, Greenlund AC, Campbell D, Carver-Moore K, DuBois RN, Clark R, Aguet M, Schreiber RD. Targeted disruption of the Stat1 gene in mice reveals unexpected physiologic specificity in the JAK-STAT signaling pathway. *Cell* 1996; **84**: 431-442 [PMID: 8608597 DOI: 10.1016/s0092-8674(00)81288-x]

33 **Durbin JE**, Hackenmiller R, Simon MC, Levy DE. Targeted disruption of the mouse Stat1 gene results in compromised innate immunity to viral disease. *Cell* 1996; **84**: 443-450 [PMID: 8608598 DOI: 10.1016/s0092-8674(00)81289-1]

34 **Park C**, Li S, Cha E, Schindler C. Immune response in Stat2 knockout mice. *Immunity* 2000; **13**: 795-804 [PMID: 11163195 DOI: 10.1016/s1074-7613(00)00077-7]

35 **Namen AE**, Lupton S, Hjerrild K, Wignall J, Mochizuki DY, Schmierer A, Mosley B, March CJ, Urdal D, Gillis S. Stimulation of B-cell progenitors by cloned murine interleukin-7. *Nature* 1988; **333**: 571-573 [PMID: 3259677 DOI: 10.1038/333571a0]

36 **Lin Q**, Dong C, Cooper MD. Impairment of T and B cell development by treatment with a type I interferon. *J Exp Med* 1998; **187**: 79-87 [PMID: 9419213 DOI: 10.1084/jem.187.1.79]

37 **Yang X**, Khosravi-Far R, Chang HY, Baltimore D. Daxx, a novel Fas-binding protein that activates JNK and apoptosis. *Cell* 1997; **89**: 1067-1076 [PMID: 9215629 DOI: 10.1016/s0092-8674(00)80294-9]

38 **Gongora R**, Stephan RP, Zhang Z, Cooper MD. An essential role for Daxx in the inhibition of B lymphopoiesis by type I interferons. *Immunity* 2001; **14**: 727-737 [PMID: 11420043 DOI: 10.1016/s1074-7613(01)00152-2]

39 **Muromoto R**, Ishida M, Sugiyama K, Sekine Y, Oritani K, Shimoda K, Matsuda T. Sumoylation of Daxx regulates IFN-induced growth suppression of B lymphocytes and the hormone receptor-mediated transactivation. *J Immunol* 2006; **177**: 1160-1170 [PMID: 16818774 DOI: 10.4049/jimmunol.177.2.1160]

40 **Gay S**. Rheumatoid arthritis. *Curr Opin Rheumatol* 2001; **13**: 191-192 [PMID: 11333347 DOI: 10.1097/00002281-200105000-00007]

41 **Courtenay JS**, Dallman MJ, Dayan AD, Martin A, Mosedale B. Immunisation against heterologous type II collagen induces arthritis in mice. *Nature* 1980; **283**: 666-668 [PMID: 6153460 DOI: 10.1038/283666a0]

42 **Ortmann R**, Smeltz R, Yap G, Sher A, Shevach EM. A heritable defect in IL-12 signaling in B10.Q/J mice. I. In vitro analysis. *J Immunol* 2001; **166**: 5712-5719 [PMID: 11313413 DOI: 10.4049/jimmunol.166.9.5712]

43 **Yap GS**, Ortmann R, Shevach E, Sher A. A heritable defect in IL-12 signaling in B10.Q/J mice. II. Effect on acute resistance to Toxoplasma gondii and rescue by IL-18 treatment. *J Immunol* 2001; **166**: 5720-5725 [PMID: 11313414 DOI: 10.4049/jimmunol.166.9.5720]

44 **Khachigian LM**. Collagen antibody-induced arthritis. *Nat Protoc* 2006; **1**: 2512-2516 [PMID: 17406499 DOI: 10.1038/nprot.2006.393]

45 **Muromoto R**, Oritani K, Matsuda T. Tyk2-mediated homeostatic control by regulating the PGE2-PKA-IL-10 axis. *AIMS Allergy Immunol* 2021; **5**: 175-183 [DOI: 10.3934/Allergy.2021013]

46 **Itoh T**, Matsuda H, Tanioka M, Kuwabara K, Itohara S, Suzuki R. The role of matrix metalloproteinase-2 and matrix metalloproteinase-9 in antibody-induced arthritis. *J Immunol* 2002; **169**: 2643-2647 [PMID: 12193736 DOI: 10.4049/jimmunol.169.5.2643]

47 **Paniagua RT**, Chang A, Mariano MM, Stein EA, Wang Q, Lindstrom TM, Sharpe O, Roscow C, Ho PP, Lee DM, Robinson WH. c-Fms-mediated differentiation and priming of monocyte lineage cells play a central role in autoimmune arthritis. *Arthritis Res Ther* 2010; **12**: R32 [PMID: 20181277 DOI: 10.1186/ar2940]

48 **Owens B**. Multiple sclerosis. *Nature* 2016; **540**: S1 [PMID: 27902684 DOI: 10.1038/540S1a]

49 **Zamvil SS**, Steinman L. The T lymphocyte in experimental allergic encephalomyelitis. *Annu Rev Immunol* 1990; **8**: 579-621 [PMID: 2188675 DOI: 10.1146/annurev.iy.08.040190.003051]

50 **Oyamada A**, Ikebe H, Itsumi M, Saiwai H, Okada S, Shimoda K, Iwakura Y, Nakayama KI, Iwamoto Y, Yoshikai Y, Yamada H. Tyrosine kinase 2 plays critical roles in the pathogenic CD4 T cell responses for the development of experimental autoimmune encephalomyelitis. *J Immunol* 2009; **183**: 7539-7546 [PMID: 19917699 DOI: 10.4049/jimmunol.0902740]

51 **Spach KM**, Noubade R, McElvany B, Hickey WF, Blankenhorn EP, Teuscher C. A single nucleotide polymorphism in Tyk2 controls susceptibility to experimental allergic encephalomyelitis. *J Immunol* 2009; **182**: 7776-7783 [PMID: 19494301 DOI: 10.4049/jimmunol.0900142]

52 **Roda G**, Chien Ng S, Kotze PG, Argollo M, Panaccione R, Spinelli A, Kaser A, Peyrin-Biroulet L, Danese S. Crohn's disease. *Nat Rev Dis Primers* 2020; **6**: 22 [PMID: 32242028 DOI: 10.1038/s41572-020-0156-2]

53 **Wirtz S**, Neurath MF. Mouse models of inflammatory bowel disease. *Adv Drug Deliv Rev* 2007; **59**: 1073-1083 [PMID: 17825455 DOI: 10.1016/j.addr.2007.07.003]

54 **Ellinghaus D**, Ellinghaus E, Nair RP, Stuart PE, Esko T, Metspalu A, Debrus S, Raelson JV, Tejasvi T, Belouchi M, West SL, Barker JN, Kõks S, Kingo K, Balschun T, Palmieri O, Annese V, Gieger C, Wichmann HE, Kabesch M, Trembath RC, Mathew CG, Abecasis GR, Weidinger S, Nikolaus S, Schreiber S, Elder JT, Weichenthal M, Nothnagel M, Franke A. Combined analysis of genome-wide association studies for Crohn disease and psoriasis identifies seven shared susceptibility loci. *Am J Hum Genet* 2012; **90**: 636-647 [PMID: 22482804 DOI: 10.1016/j.ajhg.2012.02.020]

55 **Kobayashi T**, Siegmund B, Le Berre C, Wei SC, Ferrante M, Shen B, Bernstein CN, Danese S, Peyrin-Biroulet L, Hibi T. Ulcerative colitis. *Nat Rev Dis Primers* 2020; **6**: 74 [PMID: 32913180 DOI: 10.1038/s41572-020-0205-x]

56 **Lowes MA**, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. *Nature* 2007; **445**: 866-873 [PMID: 17314973 DOI: 10.1038/nature05663]

57 **van der Fits L**, Mourits S, Voerman JS, Kant M, Boon L, Laman JD, Cornelissen F, Mus AM, Florencia E, Prens EP, Lubberts E. Imiquimod-induced psoriasis-like skin inflammation in mice is mediated *via* the IL-23/IL-17 axis. *J Immunol* 2009; **182**: 5836-5845 [PMID: 19380832 DOI: 10.4049/jimmunol.0802999]

58 **Zheng Y**, Danilenko DM, Valdez P, Kasman I, Eastham-Anderson J, Wu J, Ouyang W. Interleukin-22, a T(H)17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. *Nature* 2007; **445**: 648-651 [PMID: 17187052 DOI: 10.1038/nature05505]

59 **Rizzo HL**, Kagami S, Phillips KG, Kurtz SE, Jacques SL, Blauvelt A. IL-23-mediated psoriasis-like epidermal hyperplasia is dependent on IL-17A. *J Immunol* 2011; **186**: 1495-1502 [PMID: 21172868 DOI: 10.4049/jimmunol.1001001]

60 **Muromoto R**, Hirao T, Tawa K, Hirashima K, Kon S, Kitai Y, Matsuda T. IL-17A plays a central role in the expression of psoriasis signature genes through the induction of IκB-ζ in keratinocytes. *Int Immunol* 2016; **28**: 443-452 [PMID: 26944069 DOI: 10.1093/intimm/dxw011]

61 **Johansen C**, Mose M, Ommen P, Bertelsen T, Vinter H, Hailfinger S, Lorscheid S, Schulze-Osthoff K, Iversen L. IκBζ is a key driver in the development of psoriasis. *Proc Natl Acad Sci U S A* 2015; **112**: E5825-E5833 [PMID: 26460049 DOI: 10.1073/pnas.1509971112]

62 **Tsoi LC**, Spain SL, Ellinghaus E, Stuart PE, Capon F, Knight J, Tejasvi T, Kang HM, Allen MH, Lambert S, Stoll SW, Weidinger S, Gudjonsson JE, Koks S, Kingo K, Esko T, Das S, Metspalu A, Weichenthal M, Enerback C, Krueger GG, Voorhees JJ, Chandran V, Rosen CF, Rahman P, Gladman DD, Reis A, Nair RP, Franke A, Barker JNWN, Abecasis GR, Trembath RC, Elder JT. Enhanced meta-analysis and replication studies identify five new psoriasis susceptibility loci. *Nat Commun* 2015; **6**: 7001 [PMID: 25939698 DOI: 10.1038/ncomms8001]

63 **Müller A**, Hennig A, Lorscheid S, Grondona P, Schulze-Osthoff K, Hailfinger S, Kramer D. IκBζ is a key transcriptional regulator of IL-36-driven psoriasis-related gene expression in keratinocytes. *Proc Natl Acad Sci U S A* 2018; **115**: 10088-10093 [PMID: 30224457 DOI: 10.1073/pnas.1801377115]

64 **Yamazaki S**, Muta T, Matsuo S, Takeshige K. Stimulus-specific induction of a novel nuclear factor-kappaB regulator, IkappaB-zeta, *via* Toll/Interleukin-1 receptor is mediated by mRNA stabilization. *J Biol Chem* 2005; **280**: 1678-1687 [PMID: 15522867 DOI: 10.1074/jbc.M409983200]

65 **Okuma A**, Hoshino K, Ohba T, Fukushi S, Aiba S, Akira S, Ono M, Kaisho T, Muta T. Enhanced

apoptosis by disruption of the STAT3-IκB-ζ signaling pathway in epithelial cells induces Sjögren's syndrome-like autoimmune disease. *Immunity* 2013; **38**: 450-460 [PMID: 23453632 DOI: 10.1016/j.immuni.2012.11.016]

66 **Muromoto R**, Tawa K, Ohgakiuchi Y, Sato A, Saino Y, Hirashima K, Minoguchi H, Kitai Y, Kashiwakura JI, Shimoda K, Oritani K, Matsuda T. IκB-ζ Expression Requires Both TYK2/STAT3 Activity and IL-17-Regulated mRNA Stabilization. *Immunohorizons* 2019; **3**: 172-185 [PMID: 31356171 DOI: 10.4049/immunohorizons.1900023]

67 **Hartupee J**, Liu C, Novotny M, Li X, Hamilton T. IL-17 enhances chemokine gene expression through mRNA stabilization. *J Immunol* 2007; **179**: 4135-4141 [PMID: 17785852 DOI: 10.4049/jimmunol.179.6.4135]

68 **Herjan T**, Hong L, Bubenik J, Bulek K, Qian W, Liu C, Li X, Chen X, Yang H, Ouyang S, Zhou H, Zhao J, Vasu K, Cockman E, Aronica M, Asosingh K, Licatalosi DD, Qin J, Fox PL, Hamilton TA, Driscoll D. IL-17-receptor-associated adaptor Act1 directly stabilizes mRNAs to mediate IL-17 inflammatory signaling. *Nat Immunol* 2018; **19**: 354-365 [PMID: 29563620 DOI: 10.1038/s41590-018-0071-9]

69 **Amatya N**, Childs EE, Cruz JA, Aggor FEY, Garg AV, Berman AJ, Gudjonsson JE, Atasoy U, Gaffen SL. IL-17 integrates multiple self-reinforcing, feed-forward mechanisms through the RNA binding protein Arid5a. *Sci Signal* 2018; **11** [PMID: 30301788 DOI: 10.1126/scisignal.aat4617]

70 **Dhamija S**, Winzen R, Doerrie A, Behrens G, Kuehne N, Schauerte C, Neumann E, Dittrich-Breiholz O, Kracht M, Holtmann H. Interleukin-17 (IL-17) and IL-1 activate translation of overlapping sets of mRNAs, including that of the negative regulator of inflammation, MCPIP1. *J Biol Chem* 2013; **288**: 19250-19259 [PMID: 23658019 DOI: 10.1074/jbc.M113.452649]

71 **Matsushita K**, Takeuchi O, Standley DM, Kumagai Y, Kawagoe T, Miyake T, Satoh T, Kato H, Tsujimura T, Nakamura H, Akira S. Zc3h12a is an RNase essential for controlling immune responses by regulating mRNA decay. *Nature* 2009; **458**: 1185-1190 [PMID: 19322177 DOI: 10.1038/nature07924]

72 **Iwasaki H**, Takeuchi O, Teraguchi S, Matsushita K, Uehata T, Kuniyoshi K, Satoh T, Saitoh T, Matsushita M, Standley DM, Akira S. The IκB kinase complex regulates the stability of cytokine-encoding mRNA induced by TLR-IL-1R by controlling degradation of regnase-1. *Nat Immunol* 2011; **12**: 1167-1175 [PMID: 22037600 DOI: 10.1038/ni.2137]

73 **Monin L**, Gudjonsson JE, Childs EE, Amatya N, Xing X, Verma AH, Coleman BM, Garg AV, Killeen M, Mathers A, Ward NL, Gaffen SL. MCPIP1/Regnase-1 Restricts IL-17A- and IL-17C-Dependent Skin Inflammation. *J Immunol* 2017; **198**: 767-775 [PMID: 27920272 DOI: 10.4049/jimmunol.1601551]

74 **Takaishi M**, Satoh T, Akira S, Sano S. Regnase-1, an Immunomodulator, Limits the IL-36/IL-36R Autostimulatory Loop in Keratinocytes to Suppress Skin Inflammation. *J Invest Dermatol* 2018; **138**: 1439-1442 [PMID: 29339122 DOI: 10.1016/j.jid.2017.12.033]

75 **Grunewald J**, Grutters JC, Arkema EV, Saketkoo LA, Moller DR, Müller-Quernheim J. Sarcoidosis. *Nat Rev Dis Primers* 2019; **5**: 45 [PMID: 31273209 DOI: 10.1038/s41572-019-0096-x]

76 **Tsutsui H**, Imamura M, Fujimoto J, Nakanishi K. The TLR4/TRIF-Mediated Activation of NLRP3 Inflammasome Underlies Endotoxin-Induced Liver Injury in Mice. *Gastroenterol Res Pract* 2010; **2010**: 641865 [PMID: 20634907 DOI: 10.1155/2010/641865]

77 **Black CA**. Delayed type hypersensitivity: current theories with an historic perspective. *Dermatol Online J* 1999; **5**: 7 [PMID: 10673450]

78 **Ghilardi N**, Kljavin N, Chen Q, Lucas S, Gurney AL, De Sauvage FJ. Compromised humoral and delayed-type hypersensitivity responses in IL-23-deficient mice. *J Immunol* 2004; **172**: 2827-2833 [PMID: 14978083 DOI: 10.4049/jimmunol.172.5.2827]

79 **Minegishi Y**. Hyper-IgE syndrome. *Curr Opin Immunol* 2009; **21**: 487-492 [PMID: 19717292 DOI: 10.1016/j.coi.2009.07.013]

80 **Russell SM**, Tayebi N, Nakajima H, Riedy MC, Roberts JL, Aman MJ, Migone TS, Noguchi M, Markert ML, Buckley RH, O'Shea JJ, Leonard WJ. Mutation of Jak3 in a patient with SCID: essential role of Jak3 in lymphoid development. *Science* 1995; **270**: 797-800 [PMID: 7481768 DOI: 10.1126/science.270.5237.797]

81 **Leonard WJ**, Lin JX, O'Shea JJ. The γ_c Family of Cytokines: Basic Biology to Therapeutic Ramifications. *Immunity* 2019; **50**: 832-850 [PMID: 30995502 DOI: 10.1016/j.immuni.2019.03.028]

82 **James C**, Ugo V, Le Couédic JP, Staerk J, Delhommeau F, Lacout C, Garçon L, Raslova H, Berger R, Bennaceur-Griscelli A, Villeval JL, Constantinescu SN, Casadevall N, Vainchenker W. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. *Nature* 2005; **434**: 1144-1148 [PMID: 15793561 DOI: 10.1038/nature03546]

83 **Flex E**, Petrangeli V, Stella L, Chiaretti S, Hornakova T, Knoops L, Ariola C, Fodale V, Clappier E, Paoloni F, Martinelli S, Fragale A, Sanchez M, Tavolaro S, Messina M, Cazzaniga G, Camera A, Pizzolo G, Tornesello A, Vignetti M, Battistini A, Cavé H, Gelb BD, Renauld JC, Biondi A, Constantinescu SN, Foà R, Tartaglia M. Somatically acquired JAK1 mutations in adult acute lymphoblastic leukemia. *J Exp Med* 2008; **205**: 751-758 [PMID: 18362173 DOI: 10.1084/jem.20072182]

84 **Druker BJ**, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, Zimmermann J, Lydon NB. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nat Med* 1996; **2**: 561-566 [PMID: 8616716 DOI: 10.1038/nm0596-561]

85 **Ferguson FM**, Gray NS. Kinase inhibitors: the road ahead. *Nat Rev Drug Discov* 2018; **17**: 353-377

[PMID: 29545548 DOI: 10.1038/nrd.2018.21]

86 **Schwartz DM**, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. *Nat Rev Drug Discov* 2017; **17**: 78 [PMID: 29282366 DOI: 10.1038/nrd.2017.267]

87 **Sonbol MB**, Firwana B, Zarzour A, Morad M, Rana V, Tiu RV. Comprehensive review of JAK inhibitors in myeloproliferative neoplasms. *Ther Adv Hematol* 2013; **4**: 15-35 [PMID: 23610611 DOI: 10.1177/2040620712461047]

88 **Dhillon S**. Tofacitinib: A Review in Rheumatoid Arthritis. *Drugs* 2017; **77**: 1987-2001 [PMID: 29139090 DOI: 10.1007/s40265-017-0835-9]

89 **Al-Salama ZT**, Scott LJ. Baricitinib: A Review in Rheumatoid Arthritis. *Drugs* 2018; **78**: 761-772 [PMID: 29687421 DOI: 10.1007/s40265-018-0908-4]

90 **Taylor PC**. Clinical efficacy of launched JAK inhibitors in rheumatoid arthritis. *Rheumatology (Oxford)* 2019; **58**: i17-i26 [PMID: 30806707 DOI: 10.1093/rheumatology/key225]

91 **Papp K**, Gordon K, Thaçi D, Morita A, Gooderham M, Foley P, Girgis IG, Kundu S, Banerjee S. Phase 2 Trial of Selective Tyrosine Kinase 2 Inhibition in Psoriasis. *N Engl J Med* 2018; **379**: 1313-1321 [PMID: 30205746 DOI: 10.1056/NEJMoa1806382]

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