

Editorial

TBK1: a potential therapeutic target in RA

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With the promising effects of biological therapies, considerable progress has been made both in treatment and in understanding the roles of cytokines in rheumatoid arthritis (RA). The identification of additional pro-inflammatory molecules and their effector functions offer possibilities for novel therapeutic modalities. Among them, innate immunity plays a critical role in inflammatory cell activation and synovial inflammation in the pathogenesis of RA. Triggering toll-like receptors (TLRs) results in production of cytokines those can enhance not only innate but also adaptive immune responses [1]. The TLRs are a family of evolutionarily conserved pattern recognition receptors (PRRs) those play a key role in sensing viral or bacterial products. Rheumatoid fibroblast-like synoviocytes (FLS) have emerged as innate immunity effectors, since FLS express TLRs and ligate these receptors, then induce the synthesis of inflammatory mediators, such as cytokines and matrix metalloproteinases (MMPs), which play pivotal roles during the destruction in rheumatoid joints [2]. TLR signaling can lead to activation of several transcription factors, including NF- κ B and interferon regulatory factors (IRFs), which have been implicated in the expression of a versatile of immune response genes [3]. Toll-like receptor 3 (TLR3) recognizes double-stranded RNA (dsRNA) which is generated during viral infection. The binding of dsRNA to TLR3 results in the coordinate activation of transcription factors those are required for gene expressions involved in the innate immunity [4]. Because the TLR3 pathway plays a key role in rheumatoid pathogenic processes through to activation of the type I interferon (IFN) system, targeting TRL3 itself or signaling generated molecules could be a new therapeutic approach for RA [5]. TLR3 ligand activates FLS resulting in the production of IFN- β and other type 1 IFN-related molecules [6]. Also, TLR3 activates a signaling pathway that leads to activation of NF- κ B or IRFs through association with

the TLR domain-containing adaptor protein inducing IFN- β (TRIF) [7]. TRIF can interact with two I-kappa B kinase (IKK)-related kinases, IKK ϵ and TRAF family member-associated NF- κ B activator (TANK)-binding kinase-1 (TBK1), which activate and translocate IRFs into nucleus to induce several target genes, including IFN- β or IFN- γ -inducible protein 10 (IP-10) [8].

In this issue of *Rheumatology*, Hammaker and colleagues report that TBK1 plays a pivotal role in TLR3-mediated IP-10 expression using FLS stimulated with the synthetic TLR3 ligand, poly(I:C) [9]. TBK1 and IKK ϵ are thought to regulate rheumatoid synovitis by activating IFN-response genes through the transcription factors, IRF3 or IRF7. They evaluated the role of TBK1 and IKK ϵ in the TLR3 signaling pathway using TBK1- or IKK ϵ -deficient FLS. Poly(I:C)-induced IRF7 gene expression was inhibited in the absence of TBK1, but not IKK ϵ . The IRF3 gene is expressed constitutively and neither TBK1 nor IKK ϵ deficiency affected IRF3 gene expression. However, IRF-3-mediated gene and protein expression of IFN- β and IP-10 was abrogated in TBK1-deficient FLS, but not in IKK ϵ -deficient FLS. Gene analysis showed that TBK1 deficiency inhibited IFN- β and IP-10 transcription without affecting mRNA stability. Their data therefore demonstrated a novel role of TBK1 as a critical regulator of TLR3-induced production of IFN- β and IP-10; a finding that has implications for the understanding of molecular mechanism of innate immune reactions in rheumatoid synovium. On the basis of these findings, they proposed that TBK1 could be an optimal therapeutic target in RA.

The mechanism by which TBK1 plays a pivotal role in TLR3-mediated IP-10 induction is still unclear. In humans, TBK1 is constitutively and ubiquitously expressed in lymphoid organs such as peripheral lymphocytes and spleen as well as in

non-lymphoid organs such as brain, kidney and skeletal muscle. IRF3 is expressed ubiquitously and is not inducible; consistent with their data [10]. Meanwhile, IRF7 is expressed at low levels in most cell types, but is strongly induced in response to various stimuli [11]. Thus, IRF7 may be involved in positive feedback of TR3-mediated regulation of type 1 IFN induction. The essential role of TBK1 in the IRF7 activation was demonstrated in TBK1-deficient FLS in their data, therefore, TBK1-mediated activation of IRF7 is required for IP-10 induction. IP-10 can activate FLS in an autocrine manner by binding CXCR3, which is constitutively expressed on the cell surface. IRFs dimerization is the key step for activation. The IRF7 dominant-negative mutation suggested that IRF3 and IRF7 form homo- and heterodimers and that these interactions are crucial for the transcriptional activation of type 1 IFN genes [12]. It is presumed that IRF7 can form a heterodimer with IRF3 and these dimers are implicated in transcriptional activation of the IP-10 gene. Therefore, it is possible that TBK1 deficiency contributes to the abortive IRF7 activation and subsequent heterodimer formation with IRF3, which resulted in the impaired transcriptional activation of IP-10.

In rheumatoid synovitis, TLR signaling pathways and molecules in the activation constitute attractive therapeutic targets. Also, it is evident that inhibiting TLRs at the levels of downstream molecules, such as IL-1 receptor-associated kinase 4 (IRAK4), may confer therapeutic efficacy in autoimmunity or inflammation [13]. IKK-related kinases, IKK ϵ and TBK1 play important roles in the induction of type 1 IFN during TLR3 activation. In this issue, Hammaker *et al.* showed that TBK1, but not IKK ϵ , was essential in the TLR3-mediated activation of IRF7 and subsequent transcription of the IP-10 gene. Production of IP-10 is associated with the pathogenesis of rheumatoid synovitis based on studies demonstrating the efficacy of IP-10

neutralization in a human autoimmune disease [14]. Thus, the kinases regulating the TLR3 downstream signaling pathways will also be important treatment targets for RA. Yet, determining how to maintain the balance between host-defense functions and the anti-inflammatory effects that may result from inhibition of TLR3 signaling remains to be a serious issue for these new therapeutics. It is desirable that these novel therapeutic approaches may find applications in the treatment of rheumatoid synovitis.

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