TBK1: a potential therapeutic target in RA

New data on a key inflammatory pathway

This editorial refers to ‘Synoviocyte innate immune responses: TANK-binding kinase 1 as a potential therapeutic target in rheumatoid arthritis’, by Deepa Hammaker et al., doi:10.1093/rheumatology/ker154, on pages 610–618.

With the advent of biologic therapies, considerable progress has been made both in treatment and in understanding the roles of cytokines in RA. The identification of additional pro-inflammatory molecules and their effect on functions offers possibilities for novel therapeutic modalities. Innate immunity plays a critical role in inflammatory cell activation and synovial inflammation in the pathogenesis of RA. The triggering of Toll-like receptors (TLRs) results in the production of cytokines that can enhance not only innate but also adaptive immune responses [1]. The TLRs are a family of evolutionarily conserved pattern recognition receptors (PRRs) that play a key role in sensing viral or bacterial products. Rheumatoid fibroblast-like synoviocytes (FLS) have emerged as innate immunity effectors, as FLS express TLRs, which when ligated induce the synthesis of inflammatory mediators such as cytokines and MMPs, that play pivotal roles in the destruction of rheumatoid joints [2]. TLR signalling can lead to activation of several transcription factors, including nuclear factor-kappa B (NF-κB) and IFN regulatory factors (IRFs), which have been implicated in the expression of a range of immune response genes [3].

TLR3 recognizes double-stranded RNA (dsRNA), which is generated during viral infection. dsRNA binding to TLR3 results in the coordinated activation of transcription factors required for gene expressions involved in the innate immunity [4]. Since the TLR3 pathway plays a key role in rheumatoid pathogenic processes through to activation of the type I IFN system, targeting TLR3 itself or TLR3 signalling-generated molecules could be a new therapeutic approach for RA [5]. TLR3 ligands activate FLS, resulting in the production of IFN-β and other type 1 IFN-related molecules [6]. Also, TLR3 activates a signalling pathway that leads to activation of NF-κB or IRFs through association with the TLR domain-containing adaptor protein inducing IFN-β (TRIF) [7]. TRIF can interact with two I-κB kinase (IKK)-related kinases, IKKε and TNF receptor-associated factor (TRAF) family member-associated NF-κB activator (TANK)-binding kinase-1 (TBK1), which activate and translocate IRFs into the nucleus to induce several target genes, including IFN-β or IFN-γ-inducible protein 10 (IP-10) [8].

In this issue of Rheumatology, Hammaker et al. [9] report that TBK1 plays a pivotal role in TLR3-mediated IP-10 expression using FLS stimulated with the synthetic TLR3 ligand, poly(I:C). TBK1 and IKKε are thought to regulate rheumatoid synovitis by activating IFN-response genes through the transcription factors, IRF3 or IRF7. Hammaker et al. [9] have evaluated the role of TBK1 and IKKε in the TLR3 signalling pathway using TBK1− or IKKε-deficient FLS. Poly(I:C)-induced IRF7 gene expression was inhibited in the absence of TBK1, but not of IKKε. The IRF3 gene is expressed constitutively and neither TBK1 nor IKKε deficiency affected IRF3 gene expression. However, IRF3-mediated gene and protein expression of IFN-β and IP-10 were abrogated in TBK1-deficient FLS, but not in IKKε-deficient FLS. Gene analysis showed that TBK1 deficiency inhibited IFN-β and IP-10 transcription without affecting mRNA stability. Their data therefore demonstrate 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 mechanisms of innate immune reactions in the rheumatoid synovium. On the basis of these findings, the authors propose that TBK1 could be an optimal therapeutic target in RA.

The mechanism by which TBK1 plays its 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 [10], which is consistent with the data of Hammaker et al. [9]. 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 TLR3-mediated regulation of type 1 IFN induction. Hammaker et al. [9] have demonstrated the essential role of TBK1 in IRF7 activation in TBK1−deficient FLS; therefore, TBK1-mediated activation of IRF7 is required for IP-10 induction. IP-10 can activate FLS in an autocrine manner by binding CXC chemokine receptor 3 (CXCR3), which is constitutively expressed on the cell surface. IRF7 dimerization is the key step for activation. The IRF7-dominant negative mutation suggests 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 abortive IRF7 activation and subsequent heterodimer formation with IRF3, which results in impaired transcriptional activation of IP-10.

In rheumatoid synovitis, TLR signalling pathways and molecules involved in 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]. The IKK-related kinases, IKKε and TBK1, play important roles in the induction of type 1 IFN during TLR3 activation. Hammaker et al. [9] have shown that TBK1, but not IKKε, is 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 signalling pathways will also be important treatment targets for RA. Yet, determining how to maintain the balance between host-defence functions and the anti-inflammatory effects that may result from inhibition of TLR3 signalling remains a serious issue for these new therapeutics. We hope that these novel therapeutic approaches find applications in the treatment of rheumatoid synovitis.

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