Addition, Retraction, Correction

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Correction to Kinase Drug Discovery – What's Next in the Field?

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Figure 3 as it appeared in the original review was missing some key Greek symbols in IKKα/β and IκBα. A corrected figure appears here:

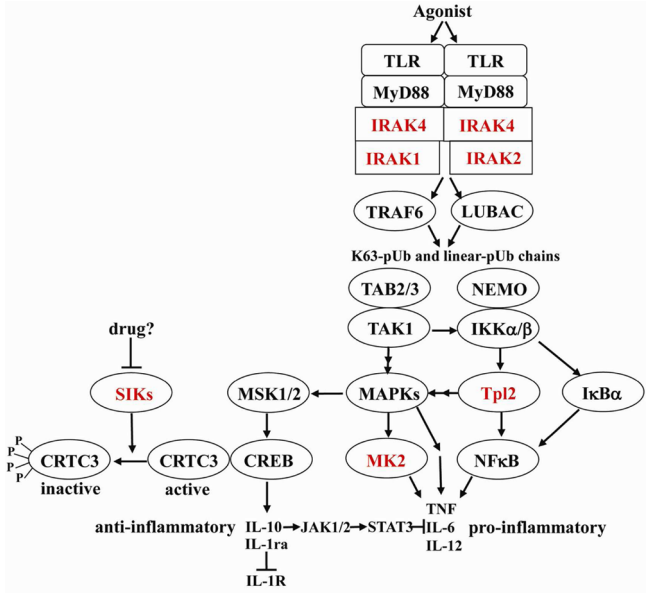

Figure 3. Simplified outline of the MyD88-signaling pathway by which TLR agonists induce the production of inflammatory mediators. Reasons why the protein kinases highlighted in red may be particularly attractive drug targets are discussed in the text. The activation of TLRs in myeloid cells recruits MyD88 and protein kinases of the IRAK family to the receptor, which induce the E3 ligase TRAF6 to produce Lys63-linked polyubiquitin (K63-pUb) chains and the E3 ligase LUBAC to produce linear pUb chains. The binding of K63-pUb chains to the TAB2 and TAB3 components of TAK1 kinase complex and K63-pUb and/or linear-pUb chains to the NEMO component of the canonical IKK complex is thought to induce conformational changes that activate these protein kinases. The IKKs phosphorylate the inhibitory IκBα component of the transcription factor NFκB and the inhibitory NFκB1/p105 component of the protein kinase Tpl2, triggering the proteasomal degradation of these inhibitors and the activation of NFκB and Tpl2. TAK1 not only initiates the activation of the IKK complex but also activates the pathways that switch on the mitogen-activated protein kinases (MAPKs) termed p38 MAP kinase and c-Jun N-terminal kinases (JNKs), while Tpl2 switches on the signaling pathway that leads to the activation of extracellular signal-regulated protein kinases 1 and 2 (ERK1, ERK2). The p38 MAP kinases, JNKs, and ERK1/2, collectively termed MAPKs in the figure, phosphorylate many proteins, which regulate the transcription, translation, processing, and secretion of inflammatory mediators, including the pro-inflammatory cytokines TNFα, IL-6, and IL-12. The protein kinase MK2, which is activated by p38α MAP kinase, stimulates post-transcriptional events required for the production of pro-inflammatory cytokines, such as TNFα and IL-6. The p38α MAP kinase and ERK1/2 also activate the protein kinases MSK1 and MSK2, which phosphorylate the transcription factor CREB, stimulating the transcription of genes encoding anti-inflammatory cytokines, such as IL-10 and IL-1ra. CREB transcriptional activity is greatly enhanced by the coactivator CRTC3 in macrophages. The phosphorylation of CRTC3, which is catalyzed by the SIK subfamily of protein kinases, prevents CRTC3 from activating CREB, restricting the production of IL-10, which can be overcome by inhibition of the SIKs. Following its secretion, IL-10 activates the IL-10 receptor by autocrine and paracrine mechanisms switching on members of the JAK family of protein kinases that phosphorylate and activate the transcription factor STAT3. These lead to the synthesis of proteins that suppress the production of pro-inflammatory cytokines and drive the conversion of classically activated M1 macrophages to regulatory M2b macrophages.

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