Interleukin-17 Promotes Autoimmunity by Triggering a Positive-Feedback Loop via Interleukin-6 Induction

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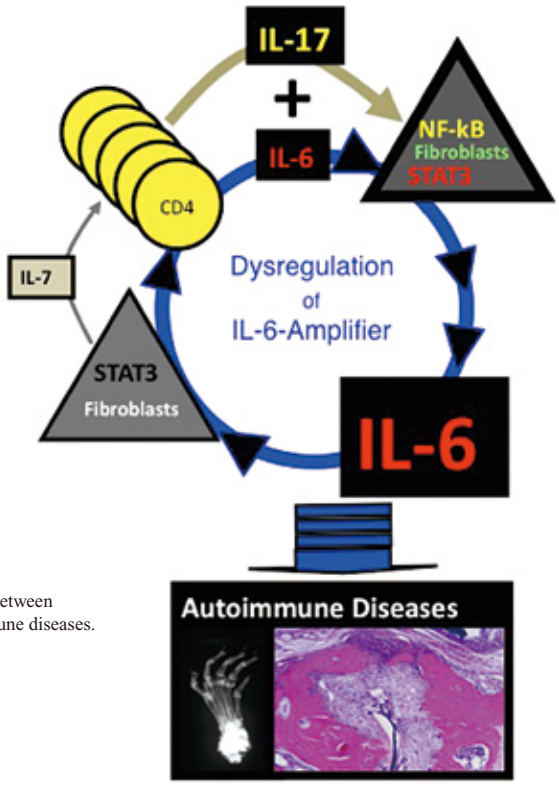
Dysregulated cytokine signaling are major contributors to a number of autoimmune diseases. Interleukin-17A (IL-17A) and IL-6 are important in many *in vivo* disorders categorized as autoimmune diseases, and IL-6 is known to induce the differentiation of effecter CD4+ T cells expressing IL-17A molecules, Th17 cells. Here we described an IL-17A-triggered positive-feedback loop of IL-6 signaling (the IL-6 amplifier), which involved the activation of the transcription factors nuclear factor (NF)-kappaB and signal transducer and activator of transcription 3 (STAT3) in fibroblasts. Importantly, dysrgulation of the IL-6 amplifier contributed to the development of arthritis. The IL-6 amplifier is one of critical players to mediate the interaction between immune system and non-immune tissues for the F759 arthritis development. Because this mechanism was also involved in experimental autoimmune encephalomyelitis (EAE) in which tissue specific T cells are involved, dysregulation of the IL-6 amplifier is likely a general etiologic process underlying other Th17 cell-mediated autoimmune diseases.



Schematic for the relationship between the IL-6 amplifier and autoimmune diseases.

Involvement of Linear Polyubiquitination of NEMO in NF-κB Activation

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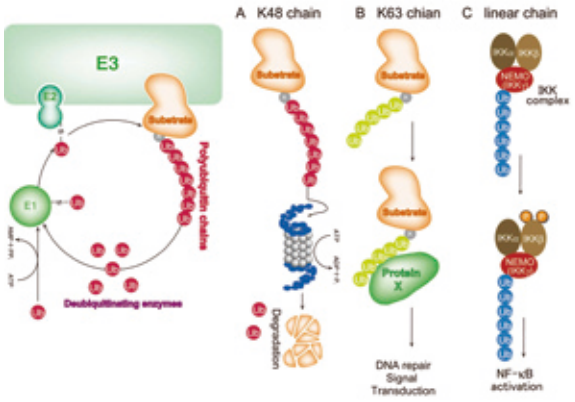

Fig. 1 The ubiquitin conjugation system

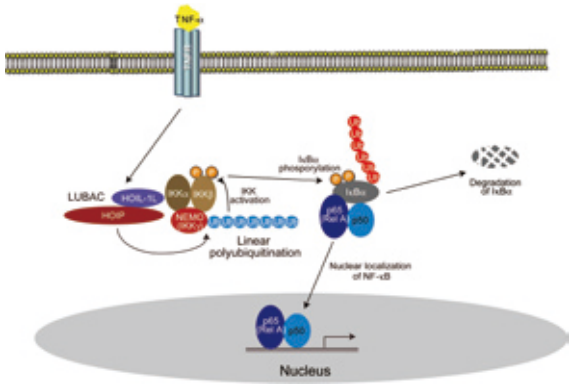

Fig. 2 Activation of NF-κB by linear polyubiquitination of NEMO

The ubiquitin conjugation system is involved in the regulation of a wide variety of biological phenomena by conjugating polyubiquitin chains onto proteins. Several type of polyubiquitin chains exist in cells and type of polyubiquitin seems to determine the mode of the regulation of proteins. We have identified a new type of chain, the linear polyubiquitin chain and a unique ubiquitin ligase complex, composed of HOIL-1L and HOIP, which selectively conjugate linear polyubiquitin chains (Figure.1). We designated the complex as LUBAC and found that LUBAC is specifically involved in NF-κB activation.

NF-κB is shown to be involved in many biological processes including inflammation and cell survival, and abnormal activation of NF-κB has been observed in several diseases including cancers and allergic diseases. In the resting state, most NF-κB resides in the cytoplasm through its binding to inhibitory proteins. When activation by various stimuli, the inhibitor proteins are phosphorylated by the IKK complex and subsequently degraded. The liberated NF-κB translocates into the nucleus and induces the expression of target genes. LUBAC has been shown to bind to NEMO in the IKK complex and to conjugate linear chains, which leads to NF-κB activation (Figure 2). Indeed, TNF-α mediated activation of NF-κB was severely impaired in primary hepatocytes and MEFs from HOIL-1L null mice. However, JNK activation was not affected. These results strongly indicated that LUBAC-mediated linear ubiquitination of NEMO is specifically involved in NF-κB activation and that small molecules that inhibit LUBAC-mediated linear chain generation may be good candidates for anti-NF-κB drugs.