IL-17–mediated phosphorylation of Regnase-1

Keywords: Regnase-1, phosphorylation, interleukin-17, drug discovery target

Summary

Regnase-1 (also known as Zc3h12a or MCPIP-1) is an endoribonuclease involved in mRNA degradation of inflammation-associated genes. Regnase-1 is inactivated in response to external stimuli through post-translational modifications including phosphorylation, yet the precise role of phosphorylation remains unknown. Hiroki Tanaka, Shizuo Akira (Host Defense, IFReC/RIMD, Osaka University), and their research group demonstrated that interleukin (IL)-17 induces phosphorylation of Regnase-1 in an Act1-TBK1/IKKi–dependent manner, especially in nonhematopoietic cells. Phosphorylated Regnase-1 is released from the endoplasmic reticulum (ER) into the cytosol, thereby losing its mRNA degradation function, which leads to expression of IL-17 target genes. By using CRISPR/Cas-9 technology, they generated Regnase-1 mutant mice, in which IL-17–induced Regnase-1 phosphorylation is completely blocked. Mutant mice (Regnase-1AA/AA and Regnase-1ΔCTD/ΔCTD) were resistant to the IL-17–mediated inflammation caused by T helper 17 (Th17) cells in vivo. Thus, Regnase-1 plays a critical role in the development of IL-17–mediated inflammatory diseases via the Act1-TBK1-IKKi axis, and blockade of Regnase-1 phosphorylation sites may be promising for treatment of Th17-associated diseases.

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Title: “Phosphorylation-dependent Regnase-1 release from endoplasmic reticulum is critical in IL-17 response.”

Journal: *The Journal of Experimental Medicine (JEM online)* on May 14, 2019.

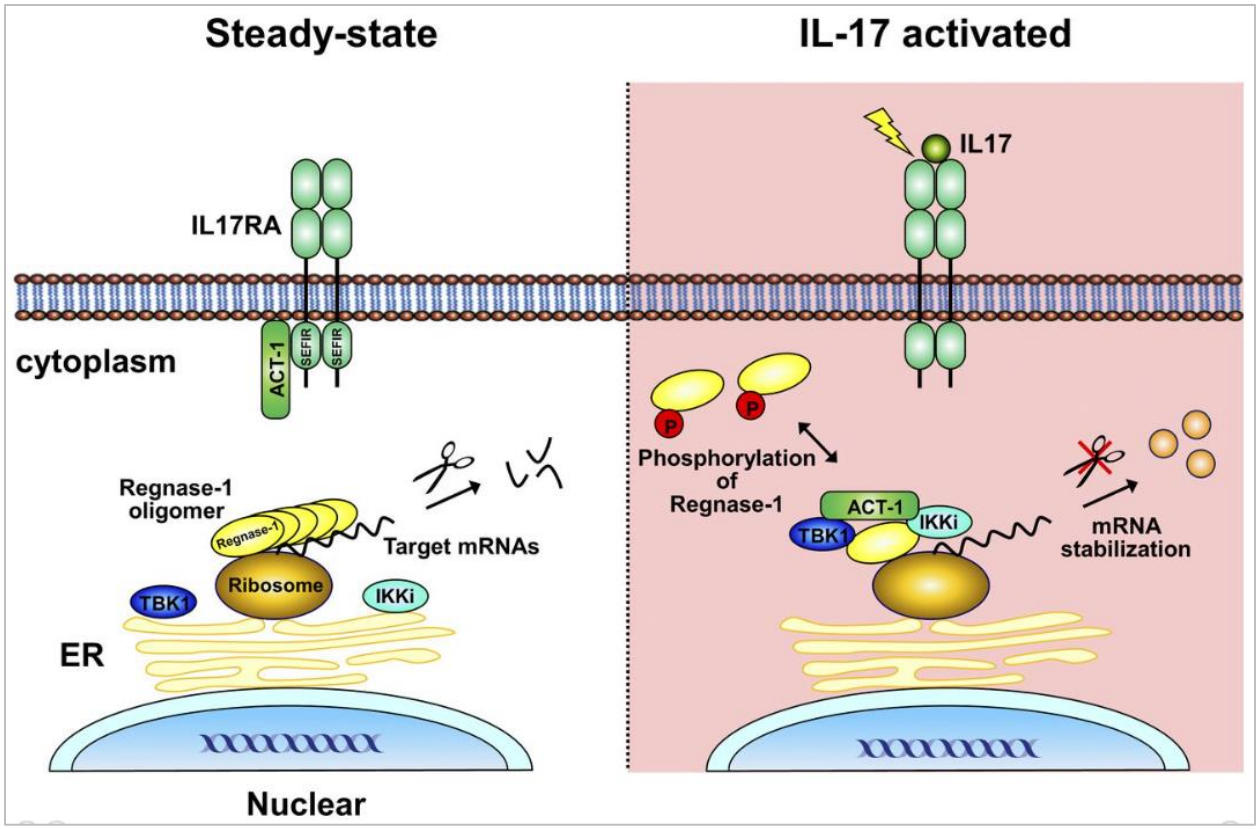

Figure: The mechanism mRNA stabilization via phosphorylation of Regnase-1.

During stimulation with interleukin 17, Regnase-1 is phosphorylated and translocated to the cytoplasm. As a result, the mRNA targeted by Regnase-1 is stabilized and translated.