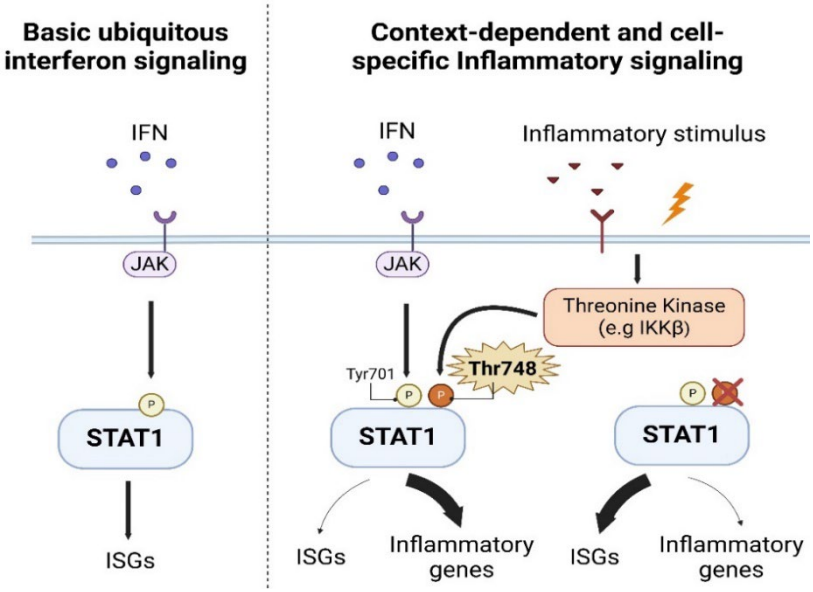
Beyond 30-year of JAKs and STATs: Threonine phosphorylation and the Yin and Yang of STAT1 in Inflammatory Responses

Keywords: Threonine; Phosphorylation; Stat1; Cytokines; Sepsis.

Interferons (IFNs) were first described over 70 years ago, followed by the identification of Janus kinase (JAK) and signal transducers and activators of transcription (STAT) proteins, which have been central to our understanding of immunity. The JAK-mediated phospho-tyrosine STAT1 is central for IFNs signaling and antiviral defense. Decades of extensive research on STAT1 have uncovered tyrosine and serine phosphorylation, and other post-translational modifications, yet they provide little insight on the potential STAT1 functionality in inflammatory responses.

In our study, we uncover the first threonine phosphorylation of the transactivation domain of STAT1, and more generally other STAT proteins. By using genetic and biochemical assays, we unveil Thr^{748} as a conserved IFN-independent phosphorylation switch in Stat1, which restricts IFN signaling and promotes innate inflammatory responses following the recognition of the bacterial-derived toxin lipopolysaccharide (LPS).



Threonine phosphorylation of STAT1 regulates the host's inflammatory responses. Stat1 displays a phosphorylation-dependent modular functionality in innate immune responses: IFN phospho-tyrosine dependent, and inflammatory phospho-threonine dependent. IFN: interferon, JAK: Janus kinase, ISGs: interferon-stimulated genes.

Our findings indicate a phosphorylation-dependent modular functionality of Stat1 in innate immune responses: IFN phospho-tyrosine dependent, and inflammatory phospho-threonine dependent, which provides deeper insight on the combinatorial signaling logic of Stat1 in shaping cell-specific and context-dependent responses. Better understanding of the Thr^{748} phosphorylation of Stat1 may offer opportunities for developing better and more specific treatment modalities for various inflammatory diseases such as sepsis without the risk of adverse effects associated with targeting the JAK signaling or total Stat1 protein.

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