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Complex actions of transcription factors in mediating cytokine biology in the immune response

Six cytokines (IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21) share the common cytokine receptor γ chain, which is mutated in humans with X-linked severe combined immunodeficiency. These cytokines all activate JAK1 and JAK3, and collectively they control a broad range of biological processes within the immune system, in part via their activation of STAT proteins. IL-2, IL-7, IL-9, and IL-15 dominantly activate STAT5A and STAT5B, IL-4 activates STAT6, and IL-21 activates primarily STAT3. IL-2 via STAT5 broadly regulates Th differentiation, promoting Th1 and Th2 differentiation via its induction of IL-12Rβ2 and IL-4Rα, and inhibiting Th17 differentiation, in part by its repression of Il6st and induction of Tbx21, as well as by potential STAT5 competition with STAT3. IL-2 also promotes Th9 differentiation, which is inhibited by IL-21, and these opposing effects of these cytokines correlate with the repression of BCL6 by IL-2 versus its induction by IL-21. Interestingly, we and others have also shown that STAT3 in combination with IRF4-BATF complexes globally mediate IL-21-dependent transcription as well as Th17 differentiation. These findings underscore the complex contributions of γ_c family cytokines and the multiple STAT proteins they regulate in controlling the immune response.

Biography

Warren J Leonard received his AB from Princeton and MD from Stanford, and now is Chief, Laboratory of Molecular Immunology and Director, Immunology Center, NHLBI. He has received many awards, including the American Association of Immunologists (AAI)-Huang Foundation Meritorious Career Award and the Honorary Lifetime Membership Award of the International Cytokine and Interferon Society. He has more than 300 publications and 19 patents. He is on multiple editorial boards, is past-President of the International Cytokine Society, a member of the Board of the Foundation for Advanced Education in the Sciences, a Fellow of the AAAS, and a member of the Institute of Medicine (IOM) of the National Academies.

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