

Interleukin-21 (IL-21), a potent immunomodulatory four- $\alpha$ -helical-bundle type I cytokine, is produced by NKT and CD4<sup>+</sup> T cells and has pleiotropic effects on both innate and adaptive immune responses. These actions include positive effects such as enhanced proliferation of lymphoid cells, increased cytotoxicity of CD8<sup>+</sup> T cells and natural killer (NK) cells, and differentiation of B cells into plasma cells. Conversely, IL-21 also has direct inhibitory effects on the antigen-presenting function of dendritic cells and can be proapoptotic for B cells and NK cells. IL-21 is also produced by Th17 cells and is a critical regulator of Th17 development. The regulatory activity of IL-21 is modulated by the differentiation state of its target cells as well as by other cytokines or costimulatory molecules. IL-21 has potent antitumor activity but is also associated with the development of autoimmune disease. IL-21 transcription is dependent on a calcium signal and NFAT sites, and IL-21 requires Stat3 for its signaling. The key to harnessing the power of IL-21 will depend on better understanding its range of biological actions, its mechanism of action, and the molecular basis of regulation of expression of IL-21 and its receptor.

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