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Interleukin-12 signalling and its effect on disease

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Interleukin-12 (IL-12) is an important cytokine that affects various diseases including cancers, infections, and autoimmune diseases. Thus, the first step in understanding cancer mechanisms and immunotherapy is to understand the signalling pathway involved with IL-12. The signalling pathway is as follows; IL-12 is a soluble cytokine that is secreted by various immune cells, such as dendritic cells, macrophages and B cells. IL-12 binds to IL-12 receptors called interleukin-12 receptor beta-1 and beta 2 subunits (IL-12Rβ1/β2). These receptors are mainly found on immune cells, such as activated T cells and NK cells. The binding of IL-12 to its receptors leads to the tyrosine phosphorylation of Janus family kinases, namely Janus kinase 2 (JAK2) and tyrosine kinase 2 (TYK2). When these kinases are phosphorylated, they can recruit an additional protein, signal transducer and activator of transcription 4 (STAT4), to the receptor and can phosphorylate STAT4 on its serine residue. The activated STAT4 then translocates to the nucleus of the cell to upregulate various genes including interferon-gamma (IFN-γ). Further, IL-12 has recently gained traction for its anti-tumorigenic properties. IL-12 signalling leads to the secretion of IFN-γ which has been shown to stunt cancer proliferation by promoting the differentiation of T helper 1 (Th1) cells and the recruitment of macrophages. It has especially been implicated in breast cancer that the single nucleotide polymorphism (SNPs) in IL-12 signalling intermediates show an increase in the risk of breast cancer. However, IL-12 is not only important in cancer but it has also been shown to be important in infections. IL-12 is produced by activated antigen-presenting cells that have come in contact with pathogenic bacteria or parasites. Studies have shown that IL12Rβ1 increases when the body is susceptible to various infections such as Salmonella infections. Additionally, IL-12 has also been linked to autoimmune diseases. IL-12 promotes the differentiation of T helper cells to Th1 via IFN- γ. Although this is beneficial in the context of infection control, it can have detrimental effects in the context of autoimmune diseases. The increased IL-12 signalling can lead to T cell-mediated pathogenesis of self-tissues. IL-12 has also been linked with inflammatory bowel disease and insulin-dependent diabetes mellitus. In conclusion, IL-12 is a vital cytokine and dysregulation in its expression and downstream signalling can lead to a multitude of different illnesses including cancers, infections and autoimmune diseases.

Keywords: Interleukin-12, Cancer, Infectious diseases, Autoimmune diseases, T helper 1 cell

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