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Interleukin-12 as a Therapeutic Target of Th1-mediated Autoimmune Diseases

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In the past it was thought that autoimmunity is mediated by antibodies and immune complexes. It has now become clear that many diseases, especially tissue specific, are T cell mediated or at least T cell dependent. The pathogenesis of cell-mediated autoimmune diseases, such as multiple sclerosis, uveitis, diabetes, arthritis, and others, is thought to be in a large measure driven by interferon-gamma-producing antigen-specific T cells polarized toward the Th1 phenotype. Interleukin-12 (IL-12), an important part of the innate immune response, is a major cytokine that drives differentiation of T cells toward this pathway and thus has a central role in the development and progression of this group of diseases. Therefore, pharmacological control of IL-12 production may be a key strategy in modulating specific immune-mediated diseases dominated by type-1 cytokine responses.

In this study we investigated the effect of auranofin (AF), an anti-rheumatic gold compound, on IL-12 production in mouse macrophages and dendritic cells, and studied whether AF-mediated inhibition of IL-12 production could regulate a cytokine profile of antigen (Ag)-primed $CD4^+$ Th cells. Treatment with AF significantly inhibited IL-12 production in lipopolysaccharide (LPS)-stimulated macrophages and also in CD40L-stimulated dendritic cells. AF-pretreated macrophages reduced their ability to induce IFN-γ and increased the ability to induce IL-4 in Ag-primed $CD4^+$ T cells. AF did not influence the cell surface expression of the class II MHC molecule and the costimulatory molecules CD80 and CD86. Addition of recombinant IL-12 to cultures of AF-pretreated macrophages and $CD4^+$ T cells restored IFN-γ production in Ag-primed $CD4^+$ T cells. The *in vivo* administration of AF resulted in the inhibition of IL-12 production by macrophages stimulated *in vitro* with LPS or heat-killed *Listeria monocytogenes* (HKL), leading to the inhibition of Th1 cytokine profile

(decreased IFN-γ and increased IL-4 production) in Ag-primed $CD4^+$ T cells. These findings may explain some known effects of AF including anti-rheumatic effects and the inhibition of encephalitogenicity, and point to a possible therapeutic use of AF in the Th1-mediated immune diseases such as autoimmune diseases.

Furthermore, as a way of regulating IL-12 production, the effects of several medicinal compounds on IL-12 production are described in mouse macrophages and their action mechanisms are also discussed at the molecular levels. For example, retinoids significantly inhibited IL-12 production in lipopolysaccharide-activated macrophages through direct interaction of nuclear factor-κB and retinoid X receptors. Importantly, retinoid-mediated inhibition of IL-12 production in macrophages suppressed Th1 cytokine profile in $CD4^+$ T cells. Other compounds including sulfasalazine showed similar pattern of regulation in IL-12 production and in cytokine profile of antigen-primed $CD4^+$ T cells. These studies suggest a possible therapeutic use of those compounds in Th1 cell-mediated autoimmune diseases including rheumatic arthritis.