IL-4 abrogates T(H)17 cell-mediated inflammation by selective silencing of IL-23 in antigen-presenting cells

Emmanuella Guenova, Yuliya Skabytska, Wolfram Hoetzenecker, Günther Weindl, Karin Sauer, Manuela Tham, Kyu-Won Kim, Ji-Hyeon Park, Ji Hae Seo, Desislava Ignatova, Antonio Cozzio, Mitchell P Levesque, Thomas Volz, Martin Köberle, Susanne Kaesler, Peter Thomas, Reinhard Mailhammer, Kamran Ghoreschi, Knut Schäkel, Boyko Amarov, Martin Eichner, Martin Schaller, Rachael A Clark, Martin Röcken & Tilo Biedermann

Interleukin 4 (IL-4) can suppress delayed-type hypersensitivity reactions (DTHRs), including organ-specific autoimmune diseases in mice and humans. Despite the broadly documented antiinflammatory effect of IL-4, the underlying mode of action remains incompletely understood, as IL-4 also promotes IL-12 production by dendritic cells (DCs) and IFN-γ-producing T(H)1 cells in vivo. Studying the impact of IL-4 on the polarization of human and mouse DCs, we found that IL-4 exerts opposing effects on the production of either IL-12 or IL-23. While promoting IL-12-producing capacity of DCs, IL-4 completely abrogates IL-23. Bone marrow chimeras proved that IL-4-mediated suppression of DTHRs relies on the signal transducer and activator of transcription 6 (STAT6)-dependent abrogation of IL-23 in antigen-presenting cells. Moreover, IL-4 therapy attenuated DTHRs by STAT6- and activating transcription factor 3 (ATF3)-dependent suppression of the IL-23/T(H)17 responses despite simultaneous enhancement of IL-12/TH1 responses. As IL-4 therapy also improves psoriasis in humans and suppresses IL-23/T(H)17 responses without blocking IL-12/T(H)1, selective IL-4-mediated IL-23/T(H)17 silencing is promising as treatment against harmful inflammation, while sparing the IL-12-dependent T(H)1 responses.