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Effect of marine compounds on autoimmune arthritis

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Introduction: Rheumatoid arthritis is characterized by the chronic inflammation of the synovial membrane of joints resulting cell interactions induce proinflammatory cytokine production which in turn activates the release of proteases leading to bone and cartilage destruction.

Purpose of the study: Modulation of inflammatory cytokines by marine sponge products represents a possible approach to the pharmaceutical prevention and treatment of Rheumatoid arthritis. New treatments could use the effects of Th17 cells on the function of regulatory T cells. IL-17, TNF- α, IL-6 and IL-1 not only promote inflammation but also inhibit regulatory T cell functions. IL-17 appears a novel target in T cell-mediated inflammatory disease, playing a role upstream in the pathologic process. Use of IL-17 inhibitors could be a way to control first inflammation but also to restore regulatory T cell functions.

Methods & Materials: In our laboratory we have screened compounds purified from marine sponge collected at Andaman and Nicobar islands for anti-collagen antibody response and anti-proliferative activity using radiolabelled thymidine. We estimated the levels of IL-17, TNF-α, IL-1β and IL-6, IL-12, IFN-γ from T cell culture supernatants of *in vitro* and *in vivo* compounds treated arthritic C57/black mice. In addition we also observed the IL-4 levels in the above treated mice.

Results: Cytokines have been found to inhibit TH17 differentiation through various mechanisms. Both IFN- ϒ and IL-4 were recognized as suppressors of TH17 development.

Conclusion: Altered balance between immunosuppressive T_{reg} and inflammatory Th17 cells appears to be major component in disease pathogenesis.

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Proinflamatory control of skeletogenic signaling pathways

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Impaired bone homeostasis contributes to development of osteopenia, osteolysis and joint erosions during the rheumatoid arthritis (RA). On the other hand, bone morphogenetic proteins (BMP) and their intracellular mediators Smad proteins, are crucially important regulators of bone formation and regeneration. Using in vitro tissue culture approaches we showed that activation of NF-κB pathway with proinflammatory cytokines IL-1β and TNFα inhibits osteogenic differentiation of pluripotent mesenchymal precursor cells through Smad7-independent inhibition of Smad1/5 transcriptional activity. Neither Smad1/5 phosphorylation by BMPR-Is, nor direct Smad1/5 binding to DNA into BMP target genes promoters are affected by the activation of NF-κB pathway with TNFα, or by the overexpression of NF-κB signaling components. Nevertheless, Smad1/5 transactivation and, consequently, transcription of BMP target genes is greatly reduced upon activation of NF-κB signaling with a requirement new protein synthesis. Furthermore, we found two distinct TNFα target genes that are novel potent inhibitors of BMP signaling. One of them, twist family BHLH transcription factor 1 (TWIST1) is a transcriptional target of NF-κB and has been implicated into repression of RUNX2 driven osteogenesis. Another one, KLF10/TIEG is induced by TNFα in NF-κB-independent manner. shRNA mediated knockdown of the expression of each of these BMP signaling repressors results in partial rescue of BMP-Smad-driven transcription from inhibition by TNFα. We generated crosses of BMP reporter mice with p65/RelA knockout mice and found that NF-κB (most likely, via TWIST1) controls the intensity and the duration of BMP signals in vivo already during the embryogenesis. Thus, our data demonstrate TIEG1 and TWIST1 as transcriptional repressors of BMP-Smad signaling and as the central candidates responsible for proinflammatory control of osteogenic program possibly also involved in the development of osteolysis and joint erosions during the RA.

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