IL-17A NEUTRALIZING ANTIBODY REGULATES MONOSODIUM URATE CRYSTAL-INDUCED GOUTY INFLAMMATION

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Introduction: Gout is a paradigm of acute, self-limited inflammation caused by increased blood uric acid levels (hyperuricemia) and the deposition of monosodium urate (MSU) crystals within intra-and/or peri-articular areas, which leads to excruciating pain and inflammatory processes. During the progression of the inflammatory response and gouty attack, MSU crystals induce a massive leukocyte infiltration into the joint cavity followed by monocytes/macrophages that, in turn, phagocytose MSU deposits resulting in membranolytic and inflammasome activation, generation of oxygen derived free radicals, release of lysosomal enzymes, prostaglandin E_2, and pro-inflammatory interleukins (mainly IL-1α, IL-6and TNF-α). However, it is still unclear how this process is being regulated and which molecular mechanisms are detrimental for gouty inflammation onset. In this context, emerging evidences support the view that systemic differentiation of Th17cells and their in-situ infiltration as one of the potential mechanisms by which these cells, and their main product IL-17, cause damage to the target tissues. The detrimental role of IL-17in gouty onset and progression have convinced us that targeting IL-17, by a neutralizing antibody strategy (IL-17Ab), could provide novel insights helpfully for a future potential treatment of gouty inflammation.

Materials and methods: Joint inflammation was induced by the intra-articular (i.a.) administration of MSU (200 μg/20 μl). Animals from IL-17Ab-treated groups received 1, 3and 10 μg (i.a.) in 20 μl of neutralizing antibody 30 minutes after MSU administration. Thereafter, joints (R and L) from different experimental conditions were scored macroscopically and knee joint oedema determined with a caliper. Histological analyses (H&E) and myeloperoxidase assay (MPO) were conducted at the 18h time-point (peak of inflammation) to evaluate leukocyte infiltration and activation. To evaluate the participation of Th17cells in gouty inflammation, we successfully detected circulating lymphocytes intracellularly positive for IL-17by flow cytometry and, in situ, the level of ~40 pro/anti-inflammatory cyto-chemokines by ElisaSpot assay.

Results: Treatment with IL-17Ab revealed a dose-dependent reduction of joint inflammation scores with maximal inhibition at 10 μg/20 μl. The neutralizing antibody was also able to significantly reduce leukocytes infiltration and MPO activity that were probably related to its ability to modulate the expression of the main pro-inflammatory cyto-chemokines such as IL-1α, IL-1β, IL-16, TREM-1, C5a, MIP-1α, MIP-2, MCP5and KC. Moreover, we found that the percentage of Th17(but not Treg) cells was increased in peripheral blood of gouty mice and positively modulated after IL-17Ab treatment.

Discussion and conclusion: The results of this study shown, for the first time, that the i.a. injection of MSU crystals stimulates *in vivo* production of Th17cells and related inflammatory cyto-chemokines in experimental acute gouty inflammation. In addition, we have provided evidences that the administration of a neutralizing monoclonal antibody against IL-17attenuates joint symptoms, swelling and leukocytes infiltration to the inflamed tissue with a systemic positive modulation of circulating Th17cells possibly providing a new strategy for the treatment of gout and/or gouty arthritis.