NLRP3 inflammasome as a possible therapeutic target in a mouse model of psoriasis induced by imiquimod

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The NLRP3 inflammasome is an intracytoplasmic protein complex involved in several diseases, especially those characterized by a chronic inflammation. The activation of NLRP3 induces the release of caspase-1 and the consequent cleavage and discharge of IL-1β and IL-18 in many tissues and cell types, including keratinocytes.
Psoriasis is an immune-mediated skin disorder characterized by chronic inflammation and accompanied by erythematous scaly plaques. Topical application of imiquimod (IMQ), a Toll-like receptor 7 ligand, induces psoriatic lesions, erythema, acanthosis and inflammatory infiltrate in mice. Since inflammation exacerbates psoriatic disease, the aim of our study was to evaluate the possible involvement of NLRP3 inflammasome in IMQ-induced psoriatic disorder and to investigate whether its blockade might ameliorate skin psoriatic lesions.
C57BL/6J mice (n=28) were shaved on the back and received a topical application of 5% IMQ cream (Psoriasis group) or vaseline (Sham Psoriasis group) for 7 consecutive days. Animals from both groups were randomly treated with BAY 11-7082 (20 mg/kg i.p), an inflammasome blocking agent, or with its vehicle (1 ml/kg/ip) 30 minutes after the first administration of IMQ. The treatment with BAY 11-7082 or vehicle was repeated at day 3 and day 5. Mice were killed on day 7 after the last administration of IMQ or vaseline, and skin samples were obtained to evaluate protein expression of pNF-kB, TNF-α, IL-6, pSTAT-3, IL-1β and Caspase-1. Furthermore, skin samples were used for histological analysis and immunohistochemical staining for NLRP3.
All psoriatic animals treated with vehicle, exhibited an increased expression of the transcriptional factors pNF-kB and pSTAT-3 and of the pro-inflammatory cytokines IL-6, IL-1β and TNF-α. Caspase-1 was also increased, thus suggesting pyroptosis activation.
Treatment with BAY 11-7082 reduced the expression of pNF-kB, pSTAT-3, IL-6 and TNF-α compared to psoriatic animals treated with vehicle ($p<0.05$). BAY 11-7082 blunted the expression of Caspase-1 and IL-1β, thus confirming the blockade of the NLRP3 inflammasome in our model. Histological evaluations indicated that NLRP3 blockade reduced skin inflammation and psoriatic lesions as well as acanthosis, improving the course of the disease.
These results demonstrate that NLRP3 inflammasome plays an important role in inflammation during psoriasis and that its blockade might represent a promising novel therapeutic approach to ameliorate psoriatic lesions.