The NLRP3 inflammasome pathway is activated in sarcoidosis and involved in granuloma formation

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This pilot study underscores a pivotal role for the NLRP3 inflammasome and MIR-223 in the pathogenesis of sarcoidosis. A beneficial effect of a NLRP3 inflammasome pathway inhibitor and an anti-IL-1β antibody on granuloma formation is demonstrated.


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ABSTRACT Sarcoidosis is a disease characterised by granuloma formation. There is an unmet need for new treatment strategies beyond corticosteroids. The NLRP3 inflammasome pathway is expressed in innate immune cells and senses danger signals to elicit inflammatory interleukin (IL)-1β; it has recently become a druggable target. This prompted us to test the role of the NLRP3 inflammasome and IL-1β pathway in granuloma formation and sarcoidosis.

19 sarcoid patients and 19 healthy volunteers were recruited into this pilot study. NLRP3 inflammasome activity was measured in bronchoalveolar lavage (BAL) cells and lung and skin biopsies using immunohistochemistry, Western blot, reverse-transcriptase PCR and ELISA. For in vivo experiments we used the trehalose 6,6'-dimycolate-granuloma mouse model and evaluated lung granuloma burden in miR-223 knockout and NLRP3 knockout mice, as well as the treatment effects of MCC950 and anti-IL-1β antibody therapy.

We found strong upregulation of the NLRP3 inflammasome pathway, evidenced by expression of activated NLRP3 inflammasome components, including cleaved caspase-1 and IL-1β in lung granuloma, and increased IL-1β release of BAL cells from sarcoid patients compared to healthy volunteers (p<0.006). mRNA levels of miR-223, a micro-RNA downregulating NLRP3, were decreased and NLRP3 mRNA correspondingly increased in alveolar macrophages from sarcoid patients (p<0.005). NLRP3 knockout mice showed decreased and miR-223 knockout mice increased granuloma formation compared to wild-type mice. Pharmacological interference using NLRP3 pathway inhibitor MCC950 or an anti-IL-1β antibody resulted in reduced granuloma formation (p<0.02).

In conclusion, our data provide evidence of upregulated inflammasome and IL-1β pathway activation in sarcoidosis and suggest both as valid therapeutic targets.