Sterile Inflammation in Innate Immune Responses

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ABSTRACT

Detection of pathogen components and subsequent induction of innate immune responses, such as the production of inflammatory cytokines and type I interferon (IFN), is mediated by pattern-recognition receptor (PRR) that include Toll-like receptor (TLR), RIG-I-like receptors (RLR), C-type lectin receptor, NOD-like receptor and intracellular sensor for DNA (AIM2, DAI, IFI16 and DDX41). In addition to infectious insults, endogenous damage-associated molecular pattern molecules (DAMPs) also activate these receptors, resulting in sterile inflammation. In response to Nigericin, monosodium urate, or silica particles, NLRP3 forms the inflammasome with its adaptor protein ASC and mediates innate immune responses. Chemical compound screening revealed that tubulin polymerization inhibitors including colchicine specifically suppress NLRP3-inflammasome activation. NLRP3-inflammasome inducers cause aberrant mitochondrial homeostasis to reduce the NAD+ level, which in turn inactivates the NAD^+-dependent α-tubulin deacetylase Sirtuin 2 (SIRT2), resulting in accumulation of acetylated α-tubulin. Accumulated acetylated α-tubulin mediates ASC-NLRP3 contact to promote NLRP3-inflammasome activation. These findings indicate that, in addition to direct activation of NLRP3, the creation of optimal sites for signal transduction by microtubules is required for entire activation of the NLRP3-inflammasome.

Macrophages are categorized in two subgroups M1 and M2. Whereas M1 macrophages are proinflammatory, M2 macrophages are anti-inflammatory and also involved in tissue remodelling. Trib1 is an adaptor protein involved in protein degradation by interacting with COP1 ubiquitin ligase. Trib1 deficiency results in severe reductions of tissue-resident M2-like macrophages in various organs. Mice lacking Trib1 in haematopoietic cells show severe lipodystrophy owing to increased lipolysis, even on a normal diet. Supplementation of M2-like macrophages rescues the lipodystrophy, indicating that the lack of tissue-resident M2-like macrophages is the cause of the lipolysis. In **r**esponse to a high-fat diet, mice lacking Trib1 in hematopoietic cells show hypertriglyceridemia, glucose intolerance and insulin resistance, together with increased proinflammatory cytokine gene induction. Collectively, these results demonstrate that Trib1 is critical for adipose tissue maintenance and suppression of metabolic disorders by controlling the differentiation of tissue-resident M2-like macrophages.