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Induction of autophagy: potential implications for modulation of gouty inflammation

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Abstract

Gouty arthritis is an autoinflammatory disease that is caused by the deposition of monosodium urate (MSU) crystals in articular joints and periarticular tissues. Autophagy is an essential cellular process that maintains homeostasis and functions and has the potential to impact the progression of inflammatory diseases. However, the role of autophagy in regulating gouty inflammation remains unclear. Here, we report the induction of autophagy in macrophages by MSU crystals and synovial tissues from patients with gouty arthritis. Immunohistochemical analysis of gouty arthritis synovial tissues demonstrated punctate staining for microtubule-associated protein light chain 3-II (LC3-II), a hallmark of autophagic activation, as compared to those of osteoarthritis. LC3-II staining was positive in greater than 50% of the macrophages present and was localized mainly to the synovial lining layer. Immunoblotting analyses revealed that MSU crystals markedly increased endogenous LC3-II levels in MSU crystal-treated RAW264.7 mouse macrophages and human peripheral blood mononuclear cells (PBMCs). Confocal microscopic analyses further showed that MSU crystals enhanced the number and the intensity of LC3-II puncta, which directly correlate with autophagosome accumulation, in both parental RAW264.7 cells and RAW264.7 cells stably expressing GFP-LC3. Moreover, endogenous LC3-II levels were further increased in macrophages treated with MSU crystals in the presence of the lysosomal inhibitors E64d and Pepstatin A, indicating an active autophagic flux. Taken together, these results suggest that autophagy is associated with modulation of the inflammatory responses in gouty arthritis.