Elucidating the mechanism of NLRP3 inflammasome activity regulation by lysosomes

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Abstract

In response to bacterial invasion or cellular damage, cells sense these situations as 'danger signals' and initiate immune responses by forming a cellular protein complex called the NLRP3 inflammasome. In recent years, it has been revealed that the NLRP3 inflammasome plays a crucial role not only in infections but also in the pathogenesis of various diseases such as cancer, diabetes, lipid disorders, and neurodegenerative disorders like Alzheimer's disease. It has emerged as a promising target for novel treatments in a variety of illnesses. However, the detailed mechanisms regulating its activity, which provide the molecular basis for drug development, have remained elusive. In our recent study, our research group has uncovered that the Ragulator complex located on lysosomes controls the activity of the NLRP3 inflammasome through its interaction with HDAC6.

Background & Results

Our cells recognize foreign substances such as pathogens and crystal components like uric acid that invade the body as 'danger signals' and activate a protein complex called the 'inflammasome.' One of the representative mechanisms, the NLRP3 inflammasome, is known to be involved in various diseases such as infections, severe cases of COVID-19, gout, atherosclerosis, and Alzheimer's disease. However, the activation mechanism of this inflammasome has remained unclear. Using mice in which Lamtor1, a protein essential for maintaining the Ragulator complex, was specifically depleted in macrophages, we conducted model experiments inducing gout. We discovered that the inflammation significantly decreased in Lamtor1-deficient mice. In experiments with cultured cells derived from mouse bone marrow macrophages and human monocyte-like cell lines, we found that Lamtor1 deficiency inhibited the activation of the NLRP3 inflammasome. Through techniques such as immunoprecipitation and mass spectrometry, we identified that Lamtor1 interacts with two proteins, NLRP3 and HDAC6. Screening using a natural product library revealed that DL-all-rac-α-Tocopherol, a synthetic form of vitamin E, inhibits the interaction between Lamtor1 and HDAC6, consequently reducing the activity of the NLRP3 inflammasome. Furthermore, administering synthetic vitamin E in mice reduced the inflammation associated with gout, suggesting that the regulation of NLRP3 inflammasome activity by the Ragulator complex could be a potential therapeutic target at the physiological level.

Significance of the research and Future perspective

Our discovery of the novel pathway revealing that lysosomes regulate the activity of the NLRP3 inflammasome represents previously unknown territory. Based on our findings, new potential drug targets have emerged. Given the significant role of the NLRP3 inflammasome in various diseases such as gout, COVID-19 infections, atherosclerosis, and Alzheimer's disease, this research has the potential to contribute to the development of innovative treatments for these diverse disorders.

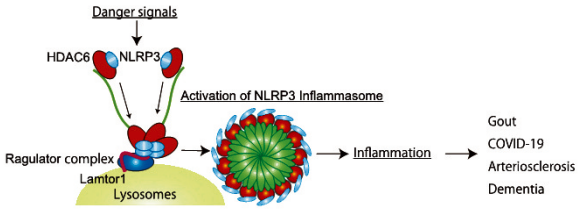

Fig1. Roles of Ragulator complex in NLRP3 inflammasome activation
The Ragulator complex expressed on the lysosomal membrane interacts with HDAC6, which augments the interactions between Lamtor1 and NLRP3, resulting in the activation of the inflammasome.

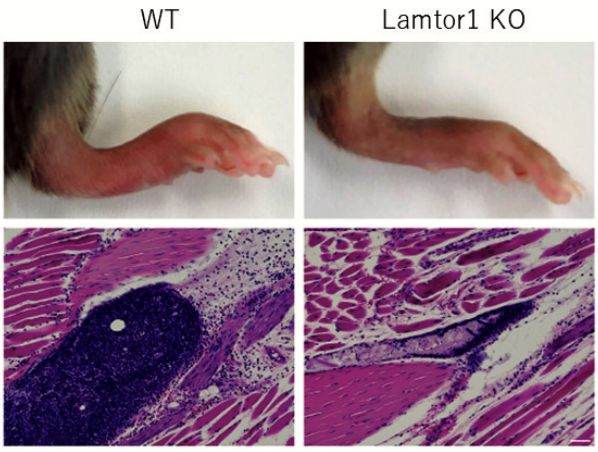

Fig2. Effects of myeloid-specific Lamtor1 deficiency in an acute gouty arthritis model.
In an acute gout arthritis model, myeloid-specific Lamtor1 knockout (KO) mice showed a reduction in gouty arthritis.

Patent

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