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# Targeting NLRP3 Inflammasome Activation: A New Mechanism Underlying the Protective Effects of Nafamostat Against Acute Pancreatitis

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**Abstract :** Nafamostat (NA), a synthetic broad-spectrum serine protease inhibitor, has been routinely employed for the treatment of acute pancreatitis (AP) and other inflammatory-associated diseases in some East Asia countries. Although the potent inhibitory activity against inflammation-related proteases such as thrombin, trypsin, kallikrein, plasmin, coagulation factors and complement factors is generally considered to be responsible for the anti-inflammatory effects of NA, precise target and molecular mechanism underlying the anti-inflammatory activity in the treatment of AP remain largely unknown yet. As an intracellular inflammatory signaling platform, the NOD-like receptor protein 3 (NLRP3) inflammasome is recently identified to be involved in the development of AP. In present study, we have revealed that NA alleviated pancreatic injury in a caerulein-induced AP model by inhibiting the NLRP3 inflammasome activation in pancreas. Mechanistically, NA interacted with HDAC6, a cytoplasmic deacetylase implicated in the NLRP3 inflammasome pathway, and efficiently abrogated the function of HDAC6. This property enabled NA to influence HDAC6 dependent NF-κB transcriptional activity and thus block NF-κB-driven transcriptional priming of NLRP3 inflammasome. Moreover, NA exerted the potential to interfere HDAC6-mediated intracellular transport of NLRP3, thereby leading to the failure of NLRP3 inflammasome activation. Our current work has provided valuable insight into the molecular mechanism underlying the immunomodulatory effect of NA in treatment of AP, highlighting its promising application in prevention of NLRP3 inflammasome-associated inflammatory pathological damage.

**Keywords :** acute pancreatitis, HDAC6, nafamostat, NLRP3 inflammasome
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