Author’s Reply

Reply to Letter Regarding Article, “NLRP3 Inflammasome as a Therapeutic Target in Myocardial Infarction”

We thank Mezzaroma, et al for their interest in our review article,1 which describes the critical role of NLRP3 inflammasomes in inflammatory responses and tissue remodeling after myocardial infarction (MI). Moreover, we congratulate them for developing a novel pharmacological inhibitor of NLRP3 inflammasomes. According to their report,2 they synthesized 16673-34-0 (5-chloro-2-methoxy-N-[2-(4-sulfamoylphenyl)ethyl]-benzamide), an intermediate in the synthesis of glyburide, that is free of the cyclohexylurea moiety involved in insulin release, and found that this compound almost completely inhibited ATP-induced IL-1β secretion in J774 macrophages and ATP-induced caspase-1 activation and cell death in HL-1 cardiomyocytes in vitro. This NLRP3 inhibitor also reduced caspase-1 activation and infarct size in a murine model of myocardial ischemia-reperfusion (I/R) injury in vivo. Furthermore, they showed that this NLRP3 inhibitor was well tolerated, with no effect on glucose levels.

Increasing evidence indicates the importance of NLRP3 inflammasomes in myocardial I/R injury. Recently, as described in our review article,1 the inflammasome-independent role of inflammasome components, such as NLRP3 and ASC, has attracted attention, especially with respect to I/R injury in several tissues. For instance, Shigeoka, et al3 reported that a reduction in renal I/R injury was observed in mice deficient in NLRP3, but not in ASC or caspase-1. Because the inflammasome is defined as a molecular platform that induces caspase-1 activation, they concluded that an NLRP3-dependent, inflammasome-independent pathway may contribute to the development of I/R injury in the kidney. Similarly, we recently found that hepatic I/R injury was significantly ameliorated in NLRP3-deficient but not in ASC or caspase-1-deficient mice.4 In this study, we further demonstrated that NLRP3 regulates chemokine-mediated neutrophil signaling and functions, which can contribute to neutrophil recruitment in the I/R liver and subsequent tissue injury.

We completely agree that the NLRP3 inhibitor recently developed by Mezzaroma, et al has great therapeutic potential for treating MI. Therefore, we would like to know whether this inhibitor could influence the inflammasome-independent functions of NLRP3. In addition, because NLRP3 inflammasomes have been shown to be involved in the process of sterile inflammation in several diseases such as gout, pseudogout, type 2 diabetes mellitus, metabolic syndrome, atherosclerosis, asbestosis, silicosis, and Alzheimer’s disease,5,6 the therapeutic effects of this inhibitor in these NLRP3 inflammasome-related diseases may be of interest and should be tested in the near future.

References


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