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Targeting gasdermin D and neutrophil mobilization for cardioprotection

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Worldwide, acute myocardial infarction (AMI) constitutes the leading cause of death, being an important cause of heart failure, higher morbidity and mortality. Despite important advances in percutaneous and surgical reperfusion, a plethora of patients who present an AMI may ultimately develop heart failure associated with a dismal prognosis. Necrotic cells may produce cytokines that activate innate immune networks, triggering an increased and sustained inflammatory response which may lead to adverse remodeling (fibrosis, scar formation and dysfunctional ventricular remodeling) resulting in postinfarction heart failure. In particular, neutrophilia is a significant sign of the inflammatory response in AMI, being associated with adverse cardiovascular events in patients with AMI [1]. Nevertheless, the mechanisms that regulate neutrophil generation and mobilization to the infarcted heart remain undetermined. Recent promising therapeutic strategies target the inhibition of selective cardinal inflammatory factors rather than the general suppression of the inflammatory response which may lead to impaired cardiac repair and augmented risk of cardiac rupture [1].

Accumulating data have highlighted the pivotal role of the inflammasome in the pathogenesis of AMI. The most widely characterized inflammasome sensor in the heart is the NACHT, LRR, and PYD domains-containing protein 3 (NLRP3), which is the intracellular multiprotein complex formed upon sensing cell debris during AMI [1]. The stimulation of the NLRP3 inflammasome triggers further myocardial damage indirectly through the release of interleukin-1β (IL-1β) and directly through the promotion of inflammatory cell death via pyroptosis [1]. Gasdermin D (GSDMD), which represents the pore-forming protein pyroptotic substrate, is a key component of the NLRP3 inflammasome, being extensively expressed in different subsets of leukocytes [2,3]. Recent data have shown that GSDMD presents a unique role in neutrophils during inflammasome activation, that is different from its role in macrophages [2,3]. However, the role of GSDMD in response to AMI is poorly understood.

In the recent study published in the Journal of Clinical Investigation [4], Jiang et al. demonstrated that GSDMD is activated early in AMI playing a critical role in the enhanced production and recruitment of neutrophils. They have shown that mice deficient in GSDMD exhibited improved LV remodeling and function, decreased neutrophil and monocyte/macrophage recruitment, and reduced remote zone fibrosis after MI as compared with wild-type mice, indicating a critical role for GSDMD in AMI and post-infarction remodeling. Furthermore, using genetic or pharmacological approaches to knockdown or inhibit GSDMD in addition to bone marrow transplantation (tissue specific knockout), Jiang et al. have provided new mechanistic insights into the molecular regulation of inflammatory response during AMI, by showing that bone marrow derived and GSDMD-dependent neutrophil production may contribute to the adverse immunopathology after MI. One recent in vitro study using ATG7-deficient cells has shown that neutrophils secrete IL-1β through N-terminal of GSDMD trafficking to neutrophil organelles, an autophagy-dependent mechanism [3], in accordance with Jiang et al. findings that GSDMD modulates IL-1β release independently of plasma membrane pores and pyroptosis in neutrophils. In contrast, Jiang et al. have shown that GSDMD deficiency triggered autophagic flux in neutrophils [4].

These novel results may be implemented in cardioprotective therapy (reduction of scar size and improvement of heart function), particularly in inhibiting GSDMD and neutrophil generation, and mobilization for the amelioration of ventricular remodeling and the reduction of heart failure after myocardial infarction.

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Declaration of competing interest

None.

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