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CYTOKINES

The inflamed heart

Myocardial infarction (MI) elicits inflammation that can lead to heart failure, but what drives this inflammation was unknown. A recent report in *Nature Medicine* shows that cardiac macrophages, responding to ischaemic cell death, trigger a type I interferon (IFN) response that fuels the fatal complications of MI.

MI causes massive synchronous cell death in the heart, leading to the release of damage-associated molecular patterns (DAMPs) that induce an innate immune response. Because previous attempts to limit post-MI-associated inflammation by targeting nuclear factor-κB were unsuccessful, the authors hypothesized that an aberrant response to self-DNA induces type I IFNs via activation of IFN-regulatory factor 3 (IRF3). In agreement with this, wild-type mice showed a robust induction of IRF3-dependent cytokines (such as *Ifnb1*) and chemokines (such as *Cxcl10*) following MI, and this was accompanied by the induction of diverse IFN-stimulated genes (ISGs). Single-cell RNA sequencing of cardiac leukocytes after MI identified a unique population of IFN-inducible, blood-derived mononuclear cells that were responsible for IRF3-dependent gene expression. Moreover, *Irf3*$^{-/-}$ mice showed a reduced accumulation of leukocytes in the heart after MI compared with wild-type mice, with a notable absence of the IFN-inducible, monocyte-derived cardiac macrophages.

By creating reporter mice in which cardiomyocytes fluoresce green (EGFP^{+}) and non-cardiomyocytes fluoresce red, the authors identified a population of CD11b^{+}F4/80^{hi}Ly6C^{low} macrophages that associated with cardiomyocyte debris following MI. These CD11b^{+}EGFP^{+} cells expressed significantly more *Ifnb1* than CD11b^{+}EGFP^{-} cells, indicating that DAMP sensing by cardiac phagocytes leads to type I IFN production.

> “DAMP sensing by cardiac phagocytes leads to type I IFN production”

To better characterize the MI-induced IFN signalling pathway, the authors measured IFN responses in mice deficient in various components of the pathway. Similar to *Irf3*$^{-/-}$ mice, mice lacking the adaptor stimulator of IFN genes (STING), its upstream DNA sensor cyclic GMP–AMP synthase (cGAS) or type I IFN receptor (IFNAR) showed reduced induction of ISGs following MI. This suggests that sensing of cytosolic DNA is responsible for the induction of an IRF3-dependent type I IFN response in the heart after MI.

The authors then tracked these events *in vivo* by injecting pregnant mice with a modified nucleotide that labels DNA in their offspring and that can be visualized by bio-orthogonal click chemistry. Cardiomyocytes retain the DNA label into adulthood, whereas in highly proliferative haematopoietic cells it becomes diluted to undetectable levels. Following MI, labelled DNA was observed in the extranuclear space of infiltrating cells around the infarct zone but not in circulating cells, suggesting uptake of cardiomyocyte DNA by heart-infiltrating cells.

Finally, the authors explored the functional significance of MI-induced IRF3 activation. Compared with wild-type mice, mice with a deficiency in IRF3, IFNAR or cGAS, or mice treated with an IFNAR-neutralizing antibody, were protected against post-MI events, showing less ventricular dilation, greater preservation of contractile function, less ventricular rupture and improved survival. Together, these data identify possible new therapeutic targets to protect from heart failure following MI.

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ORIGINAL ARTICLE King, K. R. *et al.* IRF3 and type I interferons fuel a fatal response to myocardial infarction. *Nat. Med.* http://dx.doi.org/10.1038/nm.4428 (2017)