CARDIAC REGENERATION

Macrophages produce collagen for myocardial scar formation

Macrophages directly contribute collagen to scar formation as part of heart regeneration in zebrafish and heart repair in mice. This finding by Paul Riley and colleagues develops the current paradigm of scar formation, in which collagen is generated exclusively via macrophage-mediated activation of cardiac fibroblasts into myofibroblasts.

In zebrafish, resection of the ventricle results in complete heart regeneration, without scar formation. By contrast, heart cryoinjury results in transient scar formation and delayed regeneration. In neonatal mice, the heart can regenerate during the first 7 days after birth, after which regenerative capacity is replaced by fibrotic scar formation.

In both zebrafish and mice, unbiased transcriptomics revealed an upregulation of the expression of collagens in cardiac macrophages after heart injury. In zebrafish, adoptive transfer of macrophages expressing fluorescently tagged collagen into the cryo-injured heart indicated a direct contribution of macrophage-produced collagen to scar formation. Moreover, the transfer of macrophages from resection-injured (scar-free) hearts into cryo-injured (scar-inducing) hearts resulted in excessive scarring, indicating that donor macrophages from adult zebrafish retained plasticity and could be reprogrammed by the change from a regenerative to a scar-forming environment.

Adoptive transfer of splenic macrophages expressing GFPtpz-labelled collagen from adult mice into the hearts of adult wild-type mice undergoing myocardial infarction surgery resulted in the presence of extensive GFPtpz⁺ collagen in the infarct scar. Of note, transfer of GFPtpz-collagen-labelled macrophages from adult mice into the hearts of neonatal mice undergoing cardiac injury blocked regeneration and resulted in scarring containing GFPtpz⁺ collagen. This lack of plasticity of macrophages from adult mice (in contrast to those from adult zebrafish) might partly underlie the loss of cardiac regenerative capacity in adult mice and the absence of cardiac regenerative capacity in humans.

Riley and colleagues now plan further characterization and quantification of the relative contributions of macrophages and myofibroblasts to collagen deposition in the injured hearts of zebrafish and mice. They also hope to extrapolate their research to patients with acute myocardial infarction to determine what role the direct production of collagen by macrophages might have in humans.

“Recent studies have revealed somewhat surprising roles for macrophages in the heart, such as in electrical conductance,” comments Rebecca Richardson (University of Bristol, UK), who was not involved in the study. “This study demonstrates additional surprising roles for cardiac macrophages, namely that they can directly make scar collagen themselves. Future research will determine the full functional relevance of this macrophage-derived collagen (as opposed to typical myofibroblast-derived collagen).”

Gregory B. Lim

ORIGINAL ARTICLE Simões, F. C. et al. Macrophages directly contribute collagen to scar formation during zebrafish heart regeneration and mouse heart repair. *Nat. Commun.* **11**, 600 (2020)

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“This bone marrow tolerance was potentially mediated by reduced expression of haematopoietic maintenance factor

retrospective data from 28 patients with recurrent MI, leukocytosis was also found to be lower after the recurrent MI than after the first MI.

“This line of work may help to shape recovery after MI,” says Nahrendorf. “Currently, the immune system is not targeted in standard cardiovascular therapy, which is very likely to be a missed opportunity, given that the recovery period shortly after MI may determine the disease trajectory.”

Karina Huynh

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remodelling and an increase in left ventricular ejection fraction.

“I think the benefit [of *Pdk4* deletion] is a combination of anti-remodelling plus regeneration,” says Sadek. “There are several compounds that are currently being developed that target PDK4. I believe that if these compounds reach the clinic, they will be important tools for us to use in patients with chronic heart failure.”

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