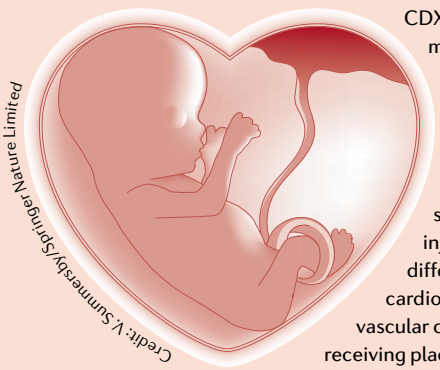
> cardiac repair through the stimulation of endogenous cardiomyocyte proliferation is attainable

Ten pigs from the AAV6-miR-199a group were followed up beyond the first month of treatment. In three of these animals, cardiac morphology and function continued to improve up to 8 weeks. However, the other seven animals died from sudden cardiac death at weeks 7–8, possibly from tachyarrhythmia events evolving into ventricular fibrillation.

"The way forward we foresee is to deliver the miRNA as a synthetic molecule, ideally through coronary catheterization," say the researchers. "The two main advantages of synthetic miRNAs compared with microRNAs expressed from viral vectors are that, first, miRNA mimics correspond only to the active miRNA (the 3p strand in our case), avoiding the unwanted effects of the other strand (5p, which could be responsible for the adverse effects observed in pigs in the long term) and, second, miRNA mimics can be dosed and are eliminated over time."

Gregory B. Lim

ORIGINAL ARTICLE Gabisonia, K. et al. MicroRNA therapy stimulates uncontrolled cardiac repair after myocardial infarction in pigs. *Nature* **569**, 418–422 (2019)



Credit: V. Summersby/Springer Nature Limited

CDX2$^+$ cells in a male mouse model of MI. After intravenous delivery, the CDX2$^+$eGFP$^+$ cells specifically homed to the site of myocardial injury, where they differentiated into cardiomyocytes and vascular cells. Mice receiving placental CDX2$^+$ cells showed improved cardiac contractility and reduced adverse remodelling after MI compared with control mice.

Taken together, these findings show that placental CDX2$^+$ cells might represent a novel source of cell therapy for cardiac regeneration. "We have successfully isolated CDX2$^+$ cells from human placentas," adds Chaudhry. "We are now working on testing their properties in vitro, and will then test them in animal models."

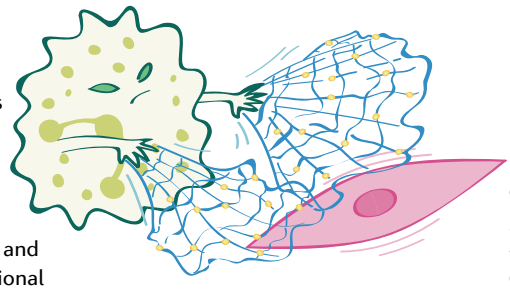
> placental CDX2$^+$ cells might represent a novel source of cell therapy for cardiac regeneration

Karina Huynh

ORIGINAL ARTICLE Vadakke-Madathil, S. et al. Multipotent fetal-derived Cdx2 cells from placenta regenerate the heart. *Proc. Natl Acad. Sci. USA* https://doi.org/10.1073/pnas.1811827116 (2019)

ATHEROSCLEROSIS

Neutrophil-driven SMC death destabilizes atherosclerotic plaques



Credit: Lara Crow/ Springer Nature Limited

Neutrophils exacerbate tissue damage and inflammation in advanced atherosclerosis by triggering smooth muscle cell (SMC) lysis and death, according to a study published in *Nature*. Oliver Soehnlein and colleagues show that lesional neutrophils release neutrophil extracellular traps (NETs) that contain histone H4, which interacts with SMCs to induce cell lysis, leading to the destabilization of atherosclerotic plaques.

To study the role of neutrophils during the transition of a stable to an unstable lesion, the researchers used a mouse model of advanced atherosclerosis. "Much to our surprise, we observed striking phenotypes on SMCs rather than macrophages when we manipulated neutrophil counts," explains Soehnlein. The number of neutrophils in atherosclerotic lesions inversely correlated with SMC counts and fibrous cap thickness, and positively correlated with necrotic core area, lesion size and plaque vulnerability. Decreasing the number of circulating neutrophils in these mice led to an increase in SMC content and fibrous cap thickness in atherosclerotic lesions, resulting in plaque stabilization. By contrast, increasing neutrophil numbers destabilized the plaques. The changes in SMC numbers were due to increased SMC death rather than proliferation. "Therefore, we shifted our focus from a neutrophil–macrophage-centred perspective to the question of how neutrophils regulate SMC survival," adds Soehnlein.

Using in vivo and in vitro assays, Soehnlein and colleagues showed that activated SMCs in atherosclerotic plaques release chemotactic factors that attract neutrophils and trigger the release of NETs containing histone H4, which has cytotoxic effects on SMCs. Extracellular histone H4 induced a type of non-programmed, receptor-independent death in SMCs via the formation of pores in the plasma membrane, which reduced membrane integrity and resulted in cell lysis. Antibody-mediated neutralization of histone H4 in mice with established atherosclerotic plaques increased SMC content and reduced lesion instability. Finally, the researchers explored therapeutic strategies to target histone H4-mediated cell lysis, and showed that disruption of the histone H4–plasma membrane interaction with a tailored peptide that binds to the N terminus of histone H4 reduced SMC death and increased plaque stability in mice with established atherosclerotic lesions.

"Atherosclerosis is the main focus of our study, but certainly the mechanisms identified here should be applicable to other forms of inflammation in which neutrophil infiltration associates with cell death, such as arthritis, inflammatory bowel disease or dementia," says Soehnlein. The therapeutic strategy for these chronic inflammatory conditions would involve preventing histone H4-induced cell death, thus reducing tissue damage and inflammation. "In addition, the mechanism of histone H4-induced cytotoxicity could also be explored in a setting in which cell death is warranted, for example, the local delivery of histone peptides in tumours," he concludes.

Irene Fernández-Ruiz

ORIGINAL ARTICLE Silvestre-Roig, C. et al. Externalized histone H4 orchestrates chronic inflammation by inducing lytic cell death. *Nature* **569**, 236–240 (2019)