IN BRIEF

CARDIOMYOPATHIES

Ketogenesis in arrhythmogenic cardiomyopathy

Sudden cardiac death is often the first manifestation of arrhythmogenic cardiomyopathy (AC), given the lack of markers to predict disease progression. A study in *Science Translational Medicine* reports that the myocardial levels of enzymes involved in ketone metabolism are increased in patients with AC, in agreement with the hypothesis that metabolic markers of increased fatty acid oxidation (FAO), such as those involved in ketone production and utilization, might provide clues for the diagnosis of AC. Specifically, the plasma levels of the ketone body β-hydroxybutyrate (β-OHB) were higher among probands than in healthy volunteers and correlated with the occurrence of major adverse cardiac events. Furthermore, plasma β-OHB concentration increased progressively with disease severity, supporting its use as a clinical marker of adverse disease progression in both patients with AC and their asymptomatic relatives.

ORIGINAL ARTICLE Song, J.-P. et al. Elevated plasma β-hydroxybutyrate predicts adverse outcomes and disease progression in patients with arrhythmogenic cardiomyopathy. *Sci. Transl Med.* **12**, eaay8329 (2020)

INTERVENTIONAL CARDIOLOGY

LVAD versus balloon pump in patients with AMI

In patients undergoing percutaneous coronary intervention for acute myocardial infarction (AMI) complicated by cardiogenic shock, use of an intravascular microaxial left ventricular assist device (LVAD) is associated with worse clinical outcomes than use of an intra-aortic balloon pump (IABP). This finding comes from a propensity-matched, registry-based, retrospective cohort study that assessed 28,304 patients, 6.2% of whom received haemodynamic support with an LVAD and 29.9% with an IABP. In the propensity-matched cohort ($n = 3,360$), LVAD use was associated with a greater risk of in-hospital death (45.0% versus 34.1%) and major bleeding (31.3% versus 16.0%) than IABP use. Importantly, these associations were consistent regardless of the timing of device placement. Additional research is required to understand the optimal device choice for these patients.

ORIGINAL ARTICLE Dhruva, S. S. et al. Association of use of an intravascular microaxial left ventricular assist device vs intra-aortic balloon pump with in-hospital mortality and major bleeding among patients with acute myocardial infarction complicated by cardiogenic shock. *JAMA* https://doi.org/10.1001/jama.2020.0254 (2020)

VASCULAR DISEASE

Cocoa might improve walking performance in PAD

Cocoa consumption improves some metrics of walking performance among old patients with peripheral artery disease (PAD), according to a new study in *Circulation Research*. Investigators of the phase II, double-blind COCOA-PAD trial randomly assigned 44 patients with PAD (mean age 72.3 years) to consume a flavanol-rich cocoa beverage or an identically appearing placebo beverage thrice daily. At the 6-month follow-up, cocoa consumption improved the 6-min walking distance measured 2.5 h after drinking the study beverage by 42.6 m compared with placebo, but did not improve the 6-min walking distance measured 24 h after study beverage intake. Furthermore, cocoa consumption did not alter maximal and pain-free treadmill walking distance or brachial artery flow-mediated dilatation but improved calf muscle perfusion and capillary density compared with placebo.

ORIGINAL ARTICLE McDermott, M. M. et al. Cocoa to improve walking performance in older people with peripheral artery disease: the Cocoa-Pad pilot randomized clinical trial. *Circ. Res.* https://doi.org/10.1161/CIRCRESAHA.119.315600 (2020)

ACUTE CORONARY SYNDROMES

Previous MI attenuates emergency haematopoiesis and inflammation

A novel mouse model of recurrent myocardial infarction (MI) reveals that a first MI can diminish the expression of haematopoietic maintenance factor in bone marrow macrophages, which leads to reduced emergency haematopoiesis and inflammatory responses to a subsequent MI. These findings, published in the *Journal of the American College of Cardiology*, indicate that haematopoietic and innate immune responses are influenced by a preceding MI.

Recurrent MI is associated with poor outcomes and high morbidity and mortality. After an MI event, neutrophils and monocytes from haematopoietic organs are recruited to the heart, in a process termed emergency haematopoiesis, to promote myocardial healing. "Because many of these immune cells have life spans that are shorter than a day, we believe that investigating bone marrow production of immune cells is important," explains Matthias Nahrendorf, the lead author of the study. The investigators developed a surgical mouse model of recurrent MI by ligating the left circumflex artery and then, 10 days later, ligating the left anterior descending coronary artery, inducing two sequential MIs in the same mouse. The numbers of myeloid cells in the blood and leukocytes in the infarct zone were lower after a recurrent MI than after a first MI.

Next, the investigators used mice joined in parabiosis, with a shared circulation, to establish that a circulating factor released after the first MI caused the diminished emergency haematopoiesis in response to a subsequent MI. This bone marrow tolerance was potentially mediated by reduced expression of haematopoietic maintenance factor in bone marrow macrophages. Finally, using

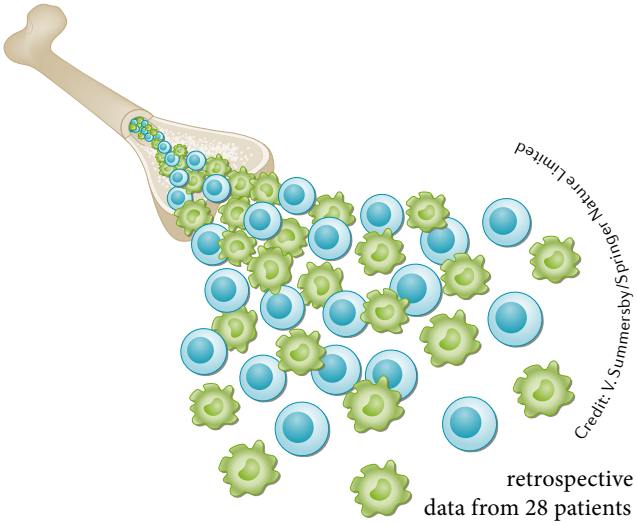
METABOLISM

Inhibiting fatty acid oxidation promotes cardiomyocyte proliferation

Mammalian hearts lose the capacity to regenerate within the first week after birth, which coincides with a metabolic shift from anaerobic glycolysis in utero to fatty acid β-oxidation postnatally. A new study published in *Nature Metabolism* shows that inhibition of fatty acid metabolism to promote oxidation of glycolysis-derived pyruvate promotes cardiomyocyte proliferation and improves left ventricular function after myocardial infarction.

"Since fatty acid utilization is known to be more pro-oxidant than glucose-derived pyruvate metabolism, we wanted to see whether forcing myocytes to use glucose-derived pyruvate would decrease oxidative stress, particularly in the form of oxidative DNA damage," says Hesham Sadek, the lead author of the study. The investigators fed neonatal mice with fatty-acid-deficient milk, which prolonged the postnatal period during which cardiomyocytes retained their proliferative capacity. However, the cells eventually entered cell cycle arrest.

Next, the researchers used a tamoxifen-inducible, cardiomyocyte-specific *Pdk4*-knockout mouse. *Pdk4* encodes pyruvate dehydrogenase kinase 4 (PDK4), and deletion of this gene selectively increases oxidation of pyruvate derived from glycolysis rather than fatty acid β-oxidation. *Pdk4* deletion resulted in reduced DNA damage and expression of DNA-damage response markers, decreased cardiomyocyte size and increased cardiomyocyte proliferation. Tamoxifen-induced deletion of *Pdk4* at 1 week after induction of myocardial infarction was associated with reductions in cardiac fibrosis, left ventricular dilatation and myocardial



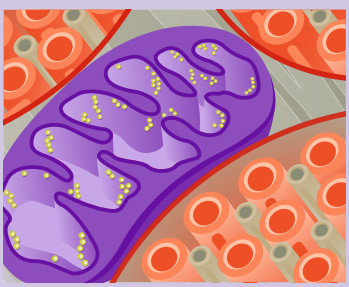
retrospective data from 28 patients with recurrent MI, leukocytosis was also found to be lower after the recurrent MI than after the first MI.

"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

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

ORIGINAL ARTICLE Cremer, S. et al. Diminished reactive hematopoiesis and cardiac inflammation in a mouse model of recurrent myocardial infarction. *J. Am. Coll. Cardiol.* **75**, 901–915 (2020)



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."

Gregory B. Lim

> the benefit [of *Pdk4* deletion] is a combination of anti-remodelling plus regeneration

ORIGINAL ARTICLE Cardoso, A. C. et al. Mitochondrial substrate utilization regulates cardiomyocyte cell-cycle progression. *Nat. Metab.* **2**, 167–178 (2020)
RELATED ARTICLE Karbassi, E. et al. Cardiomyocyte maturation: advances in knowledge and implications for regenerative medicine. *Nat. Rev. Cardiol.* https://doi.org/10.1038/s41569-019-0331-x (2020)

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.

> This lack of plasticity of macrophages from adult mice … might partly underlie the loss of cardiac regenerative capacity

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)
RELATED ARTICLES Forte, E., Furtado, M. B. & Rosenthal, N. The interstitium in cardiac repair: role of the immune–stromal cell interplay. *Nat. Rev. Cardiol.* **15**, 601–616 (2018) | Cao, J. & Poss, K. D. The epicardium as a hub for heart regeneration. *Nat. Rev. Cardiol.* **15**, 631–647 (2018)