IN BRIEF

CARDIAC RESUSCITATION

Hypothermia helps in nonshockable cardiac arrest

Moderate therapeutic hypothermia (33 °C during the first 24 h) in patients with coma who have been resuscitated from cardiac arrest with a nonshockable rhythm significantly improves survival with favourable neurological outcomes at day 90 compared with targeted normothermia. This finding comes from the HYPERION trial, an open-label, randomized, controlled trial that included 581 patients admitted to the intensive care unit with nonshockable cardiac arrest owing to cardiac or noncardiac causes. At day 90, patients who received moderate-hypothermia management had higher survival with a favourable neurological outcome (defined as Cerebral Performance Category score 1 or 2) than those who received targeted normothermia (10.2% versus 5.7%, $P = 0.04$). No differences were observed between the two groups for mortality at 90 days or the incidence of adverse events.

ORIGINAL ARTICLE Lascarrou, J.-B. et al. Targeted temperature management for cardiac arrest with nonshockable rhythm. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa1906661 (2019)

CONGENITAL HEART CONDITIONS

β-Blockers rescue cardiomyocyte division defects

A reduction in cardiomyocyte numbers owing to decreased cell division might contribute to the cardiac complications seen in adult patients with tetralogy of Fallot, according to a new study. Analysis of heart tissue from infants with tetralogy of Fallot with pulmonary stenosis showed a higher percentage of binucleated cardiomyocytes, a trait linked to cytokinesis failure, than in normal hearts. Assays in mouse models revealed that cytokinesis failure in cardiomyocytes was associated with low expression of *Ect2*, mediated by β-adrenergic receptor (β-AR) signalling. Deficiency of β-ARs in neonatal mice or treatment with the β-blocker propranolol during the neonatal phase increased *Ect2* expression and decreased cardiomyocyte binucleation, and led to increased cardiomyocyte numbers, improved cardiac function and attenuated remodelling after myocardial infarction in the adult. These findings suggest that treatment with β-blockers early after birth might rescue cytokinesis defects and prevent heart dysfunction in adulthood.

ORIGINAL ARTICLE Liu, H. et al. Control of cytokinesis by β-adrenergic receptors indicates an approach for regulating cardiomyocyte endowment. *Sci. Transl Med.* **11**, eaaw6419 (2019)

CARDIOPROTECTION

Circadian regulators as a therapeutic target in MI

Short-term targeting of the circadian regulator REV-ERB with the agonist SR9009 promotes cardiac repair after ischaemia–reperfusion injury in mice, according to a new study. These cardioprotective effects are mediated by repression of inflammatory responses. Treatment with SR9009 for just 1 day after myocardial ischaemia–reperfusion in mice increased the transcriptional repressor activity of REV-ERB and reduced the mRNA levels of cytokines and the NLRP3 inflammasome. Treated mice had less recruitment of immune cells to the infarct, reduced infarct size, less adverse remodelling and were protected against heart failure development compared with untreated mice. By contrast, SR9009 treatment in mice with REV-ERB deficiency did not impart cardioprotective benefits. Further analyses showed that cardiac fibroblasts were the cellular targets contributing to these cardioprotective effects.

ORIGINAL ARTICLE Reitz, C. J. et al. SR9009 administered for one day after myocardial ischemia-reperfusion prevents heart failure in mice by targeting the cardiac inflammasome. *Commun. Biol.* **2**, 353 (2019)

ATHEROSCLEROSIS

Pro-inflammatory atherogenic role of platelets

In addition to their well-characterized roles as mediators of thrombosis and haemostasis, platelets also have atherogenic effects by inducing monocyte migration and recruitment into atherosclerotic plaques to generate platelet–macrophage aggregates and skew macrophages to a pro-inflammatory phenotype. In patients with atherosclerotic disease, platelet activity correlates with the production of inflammatory cytokines by macrophages.

In *Ldlr*$^{-/-}$ mice fed a Western diet, the depletion of platelets attenuated macrophage accumulation in atherosclerotic plaques and reduced plaque size and necrotic area. Researchers showed that platelets drive atherosclerosis by skewing macrophages in plaques to a pro-inflammatory phenotype, characterized by increased expression of *Socs3*, which encodes suppressor of cytokine signalling 3 (SOCS3). This macrophage reprogramming results in increased production of inflammatory cytokines (including IL-1β, IL-6 and tumour necrosis factor) and impaired phagocytic capacity, which contribute to unresolved inflammation and sustained growth of the plaque.

In support of these findings from mouse studies, women with a myocardial infarction had higher levels of platelets, platelet–monocyte aggregates, SOCS3 and IL-1β than women without a myocardial infarction. In a separate cohort of patients with lower-extremity atherosclerosis, SOCS3 levels correlated with platelet activation and markers of inflammation.

"Our findings define an atherogenic role of platelets and highlight how, in the absence of thrombosis, platelets contribute to inflammation," summarize the researchers. "These data

ATHEROSCLEROSIS

HDAC9 linked to aortic calcification

A new study identifies the genetic locus encoding the histone deacetylase HDAC9 as a risk locus associated with calcification of the abdominal aorta and reveals that HDAC9 promotes the development of vascular calcification by modulating the phenotype of vascular smooth muscle cells (VSMCs). Aortic calcification is an independent risk factor for cardiovascular morbidity and death, but no drugs are currently available to prevent or treat this condition. "Understanding the genetic and molecular mechanisms of vascular calcification can help in the development of novel therapies," say the lead investigators of the study, Rajeev Malhotra and Christopher O'Donnell.

First, the investigators performed a genome-wide association meta-analysis of >9,400 individuals from the CHARGE consortium and found that variants in the *HDAC9* and *RAP1GAP* loci were associated with abdominal aortic calcification at a genome-wide level. Further analyses showed that some of the identified *HDAC9* variants were associated with increased levels of *HDAC9* transcripts. Next, the research team used cell and mouse models to determine the molecular functions of HDAC9 in vascular calcification. *HDAC9* overexpression in human aortic smooth muscle cells in vitro promoted calcification and reduced contractility, whereas HDAC9 inhibition prevented calcification and increased contractility, indicating that a high level of HDAC9 induces a phenotype switch in VSMCs

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