IN BRIEF

CARDIOMYOPATHIES

Whole-genome sequencing for HCM screening

Whole-genome sequencing (WGS) improves diagnostic accuracy in families with hypertrophic cardiomyopathy (HCM) compared with the use of targeted gene sequencing. Bagnall et al. used WGS to search for nucleotide variants in the coding regions of 184 genes, in deep intronic regions associated with RNA-splicing alterations and large genomic rearrangements, and in the mitochondrial genome in 58 patients with HCM, 14 affected family members, and two unaffected parents. WGS identified a plausible pathogenic variant in 20% of families for which previous genetic testing did not establish a molecular diagnosis. The identified variants were located in genes not included or filtered out in previous genetic testing, in noncoding regions, and in the mitochondrial genome. WGS also identified a pathogenic variant in 42% of families with no prior genetic testing. Thus, use of WGS might lead to improved diagnosis, family screening, and management of HCM.

ORIGINAL ARTICLE Bagnall, R. D. et al. Whole genome sequencing improves outcomes of genetic testing in patients with hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* **72**, 419–429 (2018)

DYSLIPIDAEMIA

LDL quality influences CAD progression

The presence of aggregation-prone LDL in plasma is associated with the risk of cardiovascular-related death in patients with coronary artery disease (CAD), independently of conventional risk factors. According to a study in which researchers used a novel method to assess the susceptibility of LDL to aggregate during ex vivo lipolysis induced by human recombinant secretory sphingomyelinase, differences in the LDL lipidome determine the susceptibility of LDL to aggregate, with aggregation-prone LDL containing more sphingolipids and fewer phosphatidylcholines than aggregation-resistant LDL. Pharmacological and genetic interventions to alter the LDL composition and lower its aggregation susceptibility led to slowed development of atherosclerosis in animal models. In humans, PCSK9 inhibition or a healthy diet induced similar changes in LDL composition that reduced its aggregation susceptibility. This study suggests that the propensity of LDL to aggregate can serve as a biomarker and that LDL aggregation can be modified by nutritional and medical interventions.

ORIGINAL ARTICLE Ruuth, M. et al. Susceptibility of low-density lipoprotein particles to aggregate depends on particle lipidome, is modifiable, and associates with future cardiovascular deaths. *Eur. Heart J.* **39**, 2562–2562 (2018)

STROKE

Lower stroke rates with PCI than with surgery

Percutaneous coronary intervention (PCI) is associated with a lower 5-year stroke rate than CABG surgery in patients with multivessel and left main coronary artery disease, according to a pooled analysis of individual patient data from 11 randomized clinical trials including a total of 11,518 patients. The lower 5-year risk of stroke with PCI than with CABG surgery (2.6% versus 3.2%; HR 0.77) was driven by a reduced risk of stroke in the 30-day post-procedural period (0.4% versus 1.1%; HR 0.33). The risk of stroke between 31 days and 5 years was similar with both procedures, and the higher risk of stroke after CABG surgery was confined to patients with multivessel disease and diabetes mellitus. With either PCI or CABG surgery, patients who had a stroke within 30 days of revascularization had a higher risk of dying within 5 years than those without a stroke.

ORIGINAL ARTICLE Head, S. J. et al. Stroke rates following surgical versus percutaneous coronary revascularization. *J. Am. Coll. Cardiol.* **72**, 386–386 (2018)

CARDIAC REGENERATION

Stem-cell therapy restores heart function after MI in macaques

Cardiomyocytes derived from human embryonic stem cells (hESC-CMs) injected into the site of a myocardial infarction (MI) in macaque monkeys improves left ventricular function. However, the grafts can be associated with ventricular arrhythmias caused by abnormal electrical impulse generation.

Charles Murry and colleagues had previously shown that hESC-CMs can remuscularize the infarcted hearts of macaques, form electromechanical junctions with the native heart muscle, and beat in synchrony with the heart. The investigators sought to determine whether hESC-CMs could restore contractile function and by what mechanisms hESC-CMs might induce arrhythmias.

Large MIs were induced in macaques by 3-h occlusion of the left anterior descending coronary artery followed by reperfusion. The resulting transmural infarcts reduced left ventricular ejection fraction (LVEF) from ~69% at baseline to ~39% at 2 weeks after MI. Approximately 750 million hESC-CMs or vehicle placebo were administered 14 days after MI by surgically exposing the heart and injecting the cells into the infarct region and border zones.

At 1 month after injection, LVEF had improved significantly in the hESC-CM group compared with the control group (50.0% versus 40.5%; $P < 0.05$). Of the three macaques assessed at 3 months after injection, LVEF continued to improve in two animals that received hESC-CMs (66.0% and 61.0%), whereas LVEF remained impaired in a control animal (40.4%). "I've been in heart research since 1984," says Murry, "and this is the largest improvement I've ever seen in function of an infarcted heart."

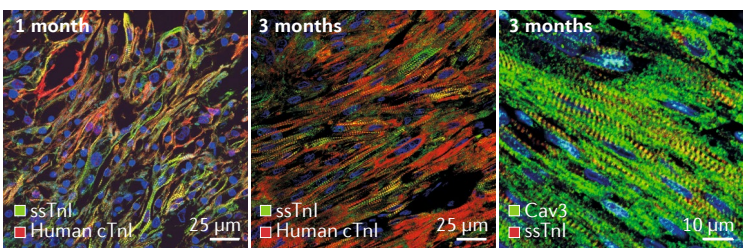
Histological analysis revealed considerable maturation of cardiomyocyte grafts (image). At 4 weeks, cardiomyocytes were quite small and misaligned, but by 3 months, cardiomyocytes were larger, aligned, and had structures resembling transverse tubules.

Although no significant difference was noted in the number, duration, or severity of arrhythmias between the two groups either before or after injection, catheter-based electrophysiology mapping studies revealed that arrhythmias in control hearts arose from a small focus of re-entry, whereas those in the hESC-CM group had features of abnormal impulse generation.

Murry and colleagues are now working on two main areas: solving the arrhythmia problem and reducing the cardiomyocyte immune profile. "If our results are successful, we will have the first treatment (aside from heart transplantation) that can treat the root cause of heart failure — that is, cardiomyocyte deficiency."

Gregory B. Lim

ORIGINAL ARTICLE Liu, Y.-W. et al. Human embryonic stem cell-derived cardiomyocytes restore function in infarcted hearts of non-human primates. *Nat. Biotech.* **36**, 597–605 (2018)
FURTHER READING Menasché, P. et al. Cell therapy trials for heart regeneration — lessons learned and future directions. *Nat. Rev. Cardiol.* https://doi.org/10.1038/s41569-018-0013-0 (2018) | Hasimoto, H. et al. Therapeutic approaches for cardiac regeneration and repair. *Nat. Rev. Cardiol.* https://doi.org/10.1038/s41569-018-0036-6 (2018)



Credit: Human embryonic stem cell-derived cardiomyocyte grafts at 1 and 3 months after injection. Cav3, caveolin 3; cTnI, cardiac troponin I; ssTnI, slow skeletal troponin I. Reprinted from Liu, Y.-W. et al. Human embryonic stem cell-derived cardiomyocytes restore function in infarcted hearts of non-human primates. *Nat. Biotech.* **36**, 597–605 (2018).