SARS-CoV-2 infection induces ferroptosis of sinoatrial node pacemaker cells

Han et al (Circ Res March 8, 2022; https://doi.org/10.1161/CIRCRESAHA.121.320518, PMID 35255712) took advantage of a hamster model and human embryonic stem cell (hESC)-derived sinoatrial node (SAN)-like pacemaker cells to explore the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on the pacemaker cells of the heart. A dual knock-in SHOX2:GFP;MYH6:mCherry hESC reporter line was generated. SARS-CoV-2 infection causes dysfunction of human SAN-like pacemaker cells and induces ferroptosis. A high content chemical screen performed to identify drugs that can inhibit SARS-CoV-2 infection and block SARS-CoV-2–induced ferroptosis identified 2 drug candidates—deferoxamine and imatinib. The authors conclude that infection of hESC-derived SAN-like pacemaker cells demonstrates ferroptosis as a potential mechanism for causing SAN dysfunction in patients with coronavirus disease 2019. Finally, the authors have identified candidate drugs that can protect the SAN cells from SARS-CoV-2 infection.

Tissue-specific multi-omics analysis of atrial fibrillation

Assum et al (Nat Commun 2022;13:441, PMID 35064145) integrated genomics, transcriptomics, and proteomics of human atrial tissue in a cross-sectional study to identify widespread effects of genetic variants on both transcript (cis-eQTL) and protein (cis-pQTL) abundance. The investigators established a novel targeted trans-QTL approach on the basis of polygenic risk scores to determine candidates for atrial fibrillation (AF) core genes. Using this approach, the authors identified 2 trans-eQTLs and 5 trans-pQTLs for AF genome-wide association study hits and elucidated the role of the transcription factor NKX2-5 as a link between the genome-wide association study single nucleotide polymorphism rs9481842 and AF. The authors conclude that the present study presents an integrative multi-omics method to uncover trans-acting networks in small data sets and provides a rich resource of atrial tissue–specific regulatory variants for transcript and protein levels for cardiovascular disease gene prioritization.

MicroRNA-365 regulates human cardiac action potential duration

Esfandyari et al (Nat Commun 2022;13:220, PMID 35017523) aimed to identify microRNAs that regulate the human cardiac action potentials (APs). Quantitative analysis of the microRNA targetomes in human cardiac myocytes identifies microRNA-365 (miR-365) as a primary microRNA that regulates repolarizing ion channels. AP recordings in patient-specific induced pluripotent stem cell–derived cardiac myocytes show that elevation of miR-365 significantly prolongs AP duration in myocytes derived from a patient with short QT syndrome, whereas specific inhibition of miR-365 normalizes pathologically prolonged AP in long QT syndrome myocytes. Transcriptome analyses in these cells support the key cardiac repolarizing channels as direct targets of miR-365. Whole-cell patch-clamp experiments confirm miR-365–dependent regulation of the slowly activating delayed rectifier K+ current. The authors conclude that miR-365 regulates human cardiac AP duration by targeting key factors of cardiac repolarization.

Inhibition of the unfolded protein response reduces arrhythmia risk after myocardial infarction

Liu et al (J Clin Invest 2021;131:e147836, PMID 34324437) tested the hypothesis that the inhibition of protein kinase R–like endoplasmic reticulum kinase (PERK) could prevent ion channel downregulation and reduce arrhythmia risk after myocardial infarction (MI). MI induced in mice by coronary artery ligation resulted in reduced ion channel levels, ventricular tachycardia (VT), and prolonged corrected intervals between the Q and T waves on the electrocardiograms (QTc intervals). The protein levels of major cardiac ion channels were decreased. MI cardiomyocytes showed significantly prolonged action potential duration and decreased maximum upstroke velocity. Cardiac-specific PERK knockout reduced electrical remodeling in response to MI, with shortened QTc intervals, fewer VT episodes, and higher survival rates. Pharmacological PERK inhibition exhibited similar effects. The authors conclude that activated PERK during MI contributed to arrhythmia risk by the downregulation of select cardiac ion channels. PERK inhibition prevented these changes and reduced arrhythmia risk.