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Ferroptosis of Pacemaker Cells in COVID-19

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Coronavirus disease 2019 (COVID-19) can lead to various cardiovascular complications, including myocardial injury, vascular injury, and thromboembolism[1]. Arrhythmias are one of the most common cardiac manifestations in COVID-19. Although tachycardias such as atrial fibrillation are often seen in the acute phase of COVID-19 patients, bradycardias are also reported in the acute phase of COVID-19[2]. More recently, long-term sequelae of COVID-19, known as Long-COVID, have been reported in various organs including the heart[3–5]. In the post-acute phase, some COVID-19 survivors suffer from palpitations due to dysregulated heart rates, atrial fibrillation, and postural orthostatic tachycardia syndrome.

In this issue of *Circulation Research*[6], Han et al. demonstrated that sinoatrial node (SAN) damage caused by direct infection of SARS-CoV-2 into SAN pacemaker cells is a potential mechanism of COVID-19-induced bradycardia. First, using a hamster model intranasally infected with SARS-CoV-2, the authors detected evidence of viral infection in SAN pacemaker cells. Under immunostaining, SARS-CoV-2 Spike protein and dsRNA were detected in $HCN4^+$ SAN cells in the heart of infected hamsters, suggesting that SARS-CoV-2 can infect SAN pacemaker cells directly *in vivo*. Second, they investigated the impact of SARS-CoV-2 infection on human SAN pacemaker cells *in vitro* using human embryonic stem cell-derived SAN-like pacemaker cells, which were generated with a newly established in-house protocol with inhibitors of FGFR, TGFβ, and STAT3. The hESC-SAN-like pacemaker cells were readily infected with SARS-CoV-2, leading to decreased expression of SAN marker genes, SAN dysfunction, and induction of ferroptosis, which was evidenced by the downregulation of GPX4. Third, they performed a drug screening using hESC-SAN-like pacemaker cells and identified deferoxamine and imatinib as potential candidate drugs to protect pacemaker cells from SARS-CoV-2 infection and ferroptosis.

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Disclosure

None.

An important aspect of this study is that SAN pacemaker cells were susceptible to SARS-CoV-2 infection *in vivo*. Although there are several reports showing that *in vitro* cardiomyocytes (CMs), especially stem cell-derived CMs, are highly susceptible to SARS-CoV-2 infection[7–9], animal models and patients' autopsy samples have not shown strong evidence of direct infection of SARS-CoV-2 for CMs[10]. Thus, COVID-19-induced myocardial injury, which is evidenced by increased serum troponin levels and one of the common cardiac representations of COVID-19, is likely to be an indirect consequence of systemic inflammation or cytokine storms rather than being caused by direct viral infection to patients' CMs. The results in this article suggest that some CM subtypes could be more susceptible to SARS-CoV-2 than typical ventricular-type CMs and show phenotypes unique to the subtypes when infected. Given that even a small percentage of damaged CMs could cause serious arrhythmic problems in the heart, subtype-specific susceptibility to SARS-CoV-2 may warrant further attention. Another important point is the potential of the two hit compounds, imatinib and deferoxamine. Imatinib was identified as inhibiting SARS-CoV-2 infection consistently in their lung and colon organoid systems[11]. Deferoxamin, which is a known inhibitor of ferroptosis, decreased SARS-CoV-2 entry as well as ferroptosis with unknown mechanisms.

There are several remaining questions for further investigation. First, as the authors acknowledged, there is no clinical report documenting infected SAN in COVID-19 patients. Although preclinical animal models and stem cell-based platforms are undoubtedly useful tools as a surrogate to model diseases with limited availability to clinical samples, it is still important to confirm their findings in human samples such as post-mortem autopsies and imaging modalities. Second, sex differences in bradycardia of COVID-19 patients would be also important although only male hamsters were used in this study. Third, it is unknown whether the SAN damage caused by SARS-CoV-2 is reversible. If the viral infection leads to ferroptosis and eventually cell death in SAN pacemaker cells, the SAN damage is likely irreversible. Thus, the patients with SAN damage would suffer from bradycardia even in the post-acute or chronic phases. This may explain a part of the relevant mechanism of heart rate dysregulation in Long-COVID. Fourth, there are other possibilities that may cause SAN damage or bradycardia in COVID-19, including hypoxemia, cytokine storm, and damage in autonomous neurons.

In conclusion, this study by Han et al. demonstrated a potential mechanism of COVID-19-induced bradycardia, in which direct infection of SARS-CoV-2 into SAN pacemaker cells was found to cause dysfunction and ferroptosis of pacemaker cells. A drug screening identified two already-existing drugs, deferoxamine and imatinib as candidates to block this process. Further studies are needed to determine whether the SAN damage can be detected in COVID-19 patients and if the proposed mechanism contritubes to dysregulated heart rates after recovery from COVID-19, which is one of the common chronic-phase sequelae of COVID-19, known as Long-COVID.

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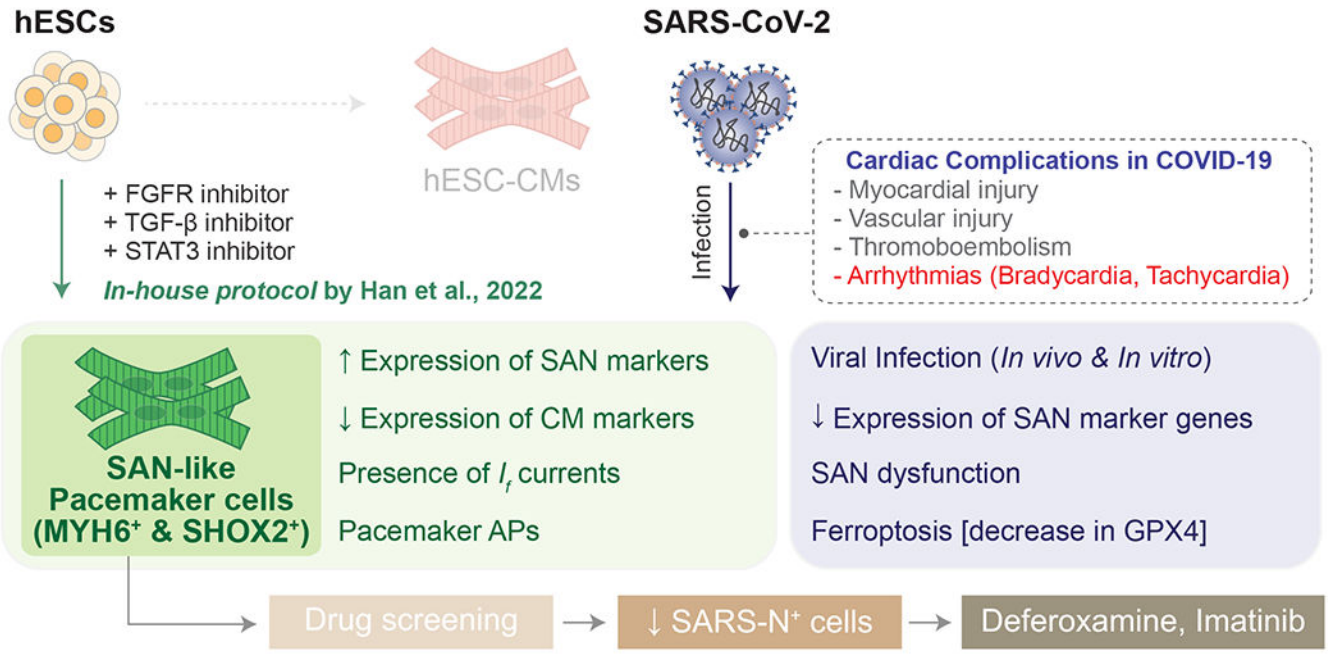

Figure. Discovery of novel anti-COVID drugs with ESC-derived SAN-like pacemaker cells.

Modulating CM differentiation protocol with chemically defined in-house protocol by Han et al led to generating a pure population of SAN-like pacemaker cells (MYH6+, SHOX2+) with electrophysiological characteristics of pacemaker cells. SAN-like pacemaker cells were susceptible to SARS-CoV-2 infection, and ferroptosis was an underlying mechanism of arrhythmias in COVID-19. Screening >1,000 FDA-approved drugs led to Deferoxamine and Imatinib being identified as novel anti-COVID-19 drugs modulating ferroptosis in SAN-like pacemaker cells. hESC, human embryonic stem cell; CM, cardiomyocyte; SAN, sinoatrial node; AP, action potential;