Polycystin-1 Regulates Atrial Fibrillation Susceptibility through Altered DNA Damage Response

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the world with a 1 in 4 lifetime risk. AF impairs cardiac function and increases the risk of thrombi, heart attack, and stroke. Although common, little is known about the full molecular mechanism driving this disease.

Patients with PC1 mutations have increased rates of arrhythmias. Furthermore, these patients have been demonstrated to have impaired DNA Damage response in kidney epithelia. This is particularly relevant because recent evidence suggests impaired DNA Damage response may play a key underlying role in AF. Therefore, understanding the interplay of PC1 mutations on atrial cardiac function and DNA damage may be a critical piece of understanding the molecular mechanisms of AF for more targeted therapeutics.

Methods

We performed burst pacing intracardiac electrophysiology in both a systemic (RC/RC) and cardiac specific (cKO) mouse model to elucidate AF susceptibility. We then performed in vitro electrophysiology measurements on atrial cardiomyocytes. We performed RNA sequencing, and finally optical mapping after DNA damage induction in PC1 siRNA knockdown human iPSC-atrial cardiomyocytes (hiPSC-aCMs).

Results

We found increased rates of atrial arrhythmias (76.9 vs 20% in RC/RC and 81.8 vs 11.1% in cKO). We then performed in vitro electrophysiology in mouse (RC/RC) and hiPSC-aCMs and found PC1 mutant cells have decreased action potential, and altered calcium handling. RNA sequencing demonstrated PC1 alters DNA Damage response pathways in atrial cardiomyocytes, which we confirmed with increased levels of DNA damage in PC1 knockdown hiPSC-aCMs following treatment with Etoposide and increased Ca^{2+} rotors.

Conclusions

We have shown, for the first time, that PC1 mutations increase AF susceptibility in multiple in vivo models and that PC1 mutations lead to impaired DNA damage response and EC coupling that combine to underly the increased AF susceptibility.

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