cardiogenetics

MDPI

Editorial

A Crossroads Junction That Leads to Heart Failure (Arrhythmogenic Cardiomyopathy): Hope for Future Therapeutics

Kadiam C. Venkata Subbaiah

Aab Cardiovascular Research Institute, Department of Medicine, University of Rochester School of Medicine & Dentistry, Rochester, NY 14642, USA; chinna_kadiam@urmc.rochester.edu; Tel.: +1-585-710-4051

Arrhythmogenic cardiomyopathy (ACM) is an inherited multifaceted cardiac disease that causes sudden cardiac death, especially in young adults and athletes. Currently, 40% of the population worldwide has been suffering from all forms of genetic cardiomyopathies mediated heart failure, in these patients left ventricular ejection fraction is not adequately tracked [1,2]. ACM defines, since its inception of families with sudden cardiac death, ventricular arrhythmias, and right ventricle malfunction followed by RV dysplasia and atrial fibrillation. With the time being, these perturbations were confirmed as arrhythmogenic right ventricle cardiomyopathy in part due to genetic mutations in desmosomal and/or non-desmosomal proteins (especially LMNA, TTN, SCN5A, RBM20, and PLN [3,4]. PLN is a 52 amino acid protein that binds to SERCA2a and inhibits its function. Furthermore, the deletion of three nucleotides in the PLN is typical for the arginine 14 in the protein (PLNR14Del) at high risk of ventricular arrhythmias in the young carriers. This single-gene mutation is responsible for causing ACM in several countries in Europe and North America [5].

Recent clinical studies have recognized that ventricular arrhythmias was the the underlying cause of death in post-COVID-19 patients due to established systemic inflammation in viral myocarditis [6,7]. There has been increasing evidence demonstrating that COVID-19-infected patients presented with ventricular tachycardia (abnormal heartbeat and/or rhythm perturbations). Therefore, arrhythmogenic cardiomyopathy is a silent and masked genetic cardiac disease and it requires medical attention in order to identify the genetic variants in myocarditis patients using the exome sequence and to guide the therapeutic options.

Currently, the available therapeutic options for either treating this disease are pharmacological or non-pharmacological. The most famous one is an implantable cardioverter defibrillator (ICD) that can prevent further life-threatening actions of fibrillation. In addition, beta-blockers and antiarrhythmic drugs (AADs) may be prescribed in the clinic. However, there were no therapeutic options, except for heart translation. Therefore, there is an imperative need to tackle all these forms of ACM, might be possible due to the genome editing technology. At the preclinical level, a recent study conducted by Francesca Stillitano's group at Mount Sinai edited the gene that reverses arrhythmia susceptibility in humanized PLN-R14 deletion in mice. They model the cardiomyopathy with global impact, and they used the strong brick to build the wall in this field [8]. Still, there is a gap in understanding the pathophysiological role of myocardial fibrosis in cardiac arrhythmia.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The author declare no conflict of interest.

Citation: Venkata Subbaiah, K.C. A Crossroads Junction That Leads to Heart Failure (Arrhythmogenic Cardiomyopathy): Hope for Future Therapeutics. *Cardiogenetics* **2023**, *13*, 31–32. https://doi.org/10.3390/cardiogenetics13010004

Received: 31 December 2022
Accepted: 3 January 2023
Published: 17 February 2023

References

1. Cadrin-Tourigny, J.; Bosman, L.P.; James, C.A. Sudden cardiac death risk prediction in arrhythmogenic right ventricular cardiomyopathy: A practical approach to navigating the challenges of prediction models. *Eur. Heart J.* **2022**, *43*, 4961–4962. [CrossRef] [PubMed]
2. Groeneweg, J.A.; Bhonsale, A.; James, C.A.; Te Riele, A.S.; Dooijes, D.; Tichnell, C.; Murray, B.; Wiesfeld, A.C.; Sawant, A.C.; Kassamali, B.; et al. Clinical Presentation, Long-Term Follow-Up, and Outcomes of 1001 Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy Patients and Family Members. *Circ. Cardiovasc. Genet.* **2015**, *8*, 437–446. [CrossRef] [PubMed]
3. Verdonschot, J.A.; Hazebroek, M.R.; Krapels, I.P.; Henkens, M.T.; Raafs, A.; Wang, P.; Merken, J.J.; Claes, G.R.; Vanhoutte, E.K.; Wijngaard, A.V.D.; et al. Implications of Genetic Testing in Dilated Cardiomyopathy. *Circ. Genom. Precis. Med.* **2020**, *13*, 476–487. [CrossRef] [PubMed]
4. Kumar, S.; Baldinger, S.H.; Gandjbakhch, E.; Maury, P.; Sellal, J.-M.; Androulakis, A.F.; Waintraub, X.; Charron, P.; Rollin, A.; Richard, P.; et al. Long-Term Arrhythmic and Nonarrhythmic Outcomes of Lamin A/C Mutation Carriers. *J. Am. Coll. Cardiol.* **2016**, *68*, 2299–2307. [CrossRef] [PubMed]
5. van der Zwaag, P.A.; van Rijsingen, I.A.; Asimaki, A.; Jongbloed, J.D.; van Veldhuisen, D.J.; Wiesfeld, A.C.; Cox, M.G.; van Lochem, L.T.; de Boer, R.A.; Hofstra, R.M.; et al. Phospholamban R14del mutation in patients diagnosed with dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy: Evidence supporting the concept of arrhythmogenic cardiomyopathy. *Eur. J. Heart Fail.* **2012**, *14*, 1199–1207. [CrossRef] [PubMed]
6. Mukhopadhyay, S.; Uppal, A.; Yusuf, J.; Muheeb, G.; Agarwal, R. COVID-19 induced ventricular tachycardia storm unmasking a clinically silent cardiomyopathy: A case report. *Eur. Heart J. Case Rep.* **2021**, *5*, ytab220. [CrossRef] [PubMed]
7. Ingul, C.B.; Grimsmo, J.; Mecinaj, A.; Trebinjac, D.; Nossen, M.B.; Andrup, S.; Grenne, B.; Dalen, H.; Einvik, G.; Stavem, K.; et al. Cardiac Dysfunction and Arrhythmias 3 Months After Hospitalization for COVID-19. *J. Am. Heart Assoc.* **2022**, *11*, e023473. [CrossRef] [PubMed]
8. Dave, J.; Raad, N.; Mittal, N.; Zhang, L.; Fargnoli, A.; Oh, J.G.; Savoia, M.E.; Hansen, J.; Fava, M.; Yin, X.; et al. Gene editing reverses arrhythmia susceptibility in humanized PLN-R14del mice: Modelling a European cardiomyopathy with global impact. *Cardiovasc. Res.* **2022**, *118*, 3140–3150. [CrossRef] [PubMed]