Of mice and men in ACM

Impact

As a genetic heart disease affecting between 1:1000 and 1:5000 people in the world every year, yet without real curative therapies or convenient diagnostic tools, arrhythmogenic cardiomyopathy (ACM) continues to exact a heavy toll on society [1]. The dearth of treatments stems, in part, from the lack of understanding of which molecular mechanisms drive the disease. Our models will help to shed light on these questions by allowing us to further investigate the altered pathways and how they contribute to the ACM phenotype. By comparing our different models to each other, as well as to those created by other groups, we can detect common cores of alterations that lie at the base of ACM and find out which changes are gene- or perhaps even mutation-specific.

In addition to elucidating disease mechanisms and furthering our basic understanding of ACM, our mouse and iPSC-based models can also serve a more immediate goal as testbeds for targeted therapies. Both the overexpression of a wild type (WT) version of the allele, as well as genome editing of the mutant allele back to the WT version are possible. The former has the advantage that a single therapy would be able to cover a host of different mutations for a specific gene, especially if the phenotype is due to haploinsufficiency. However, if there are strong dominant-negative effects of certain mutant alleles rather than haploinsufficiency, then the WT allele might not be able to buffer this. In these cases, genome editing would be required. In either case, several technological challenges need to be overcome to develop a useful gene therapy, irrespective if it's for ACM or any other cardiac (hereditary) disease. First there is the issue of delivery. The heart as an organ is notoriously hard to efficiently target compared to other organs such as the liver, which has a natural design to resorb exogenous molecules [2]. On top of that, the post-mitotic state of the heart further hinders efficient editing due to non-homologous end-joining being the dominant repair mechanism in post-mitotic cells compared to homology-directed repair, raising questions of whether a sufficient number of cells can be edited to affect positive change. Secondly, for CRISPR/Cas9-based technologies, off-target editing elsewhere in the genome remains a general concern. While recent innovations in the field such as base editing, prime editing and others have arrived promising higher efficiency and lower off-target effects, the concerns remain relevant [3]. There are more potential problems, such as (immune)toxicity and the need for a suitably close PAM site. For WT-overexpression using systems where the transgene integrates into the host genome, there are questions of where the payload will integrate and the potential to interrupt or influence expression of surrounding native genes [4].

Next to advances in the field of ACM treatments, there is also the issue of diagnosis. Despite the fact that regular exercise, under normal circumstances, is a widely recommended heart-healthy choice, in ACM patients it can drive disease progression or even cause sudden cardiac death. In fact, once diagnosed with ACM, an important yet straightforward intervention is the cessation of intensive sport activity. Thus, early screening and reliable diagnosis is of vital importance for managing disease progression. This is where identifying novel biomarkers comes in as a way to serve this need. In this thesis, we show that miR-185-5p is significantly upregulated in the plasma of ACM patients and propose it as a candidate for screening and diagnosis. The fact that miR-185-5p was also found to be elevated in ACM patients in another study [5], without being elevated in patients with cardiac amyloidosis [6], dilated cardiomyopathy [7], chronic heart failure [8] or (for miR-185) inflammatory heart disease [9] and myocardial fibrosis [10], further strengthens it as an ACM-specific biomarker candidate. However, also here the difficulties of translating academic findings to a scalable and affordable platform in the clinic rear their head. Despite being well-established when it comes to the diagnosis of various cancers, issues with replicability, detection limits, cost considerations and a lack of standardized protocols have held back the use of miRNAs as biomarkers in cardiovascular disease [11,12]. This is also reflected in the lack of clinical trials.

In conclusion, having access to therapies that address the underlying causes of ACM rather than combating the symptoms, as well as a reliable non-invasive biomarker, would present a significant improvement to the treatment and detection of ACM. This would allow us to lessen the societal burden of this disease and opens up great untapped market potential.

References

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