Mind the Gap: Genetic Variation and Personalized Therapies for Cardiomyopathies

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\textbf{Abstract}
Inherited cardiomyopathies are cardiovascular disorders that are one of the leading causes of death and are strongly associated with genetic mutations. These include hypertrophic, dilated, restrictive, as well as arrhythmogenic right ventricular cardiomyopathies. Among the patients presenting with these specific forms of cardiomyopathies, there is significant phenotypic, genotypic, and environmental heterogeneity. Over the years, the identification of the underlying mutations common to specific forms of cardiomyopathies have facilitated clinic diagnosis. However, the variation between patient genetics and phenotypes highlights the need for improved understanding of these diseases and the development of innovative treatments. To better understand the diseases, researchers are capitalizing on two innovative technologies: cardiac reprogramming and gene editing using CRISPR-Cas9. Deriving cardiomyocytes from patient blood samples and gene editing allows for the efficient generation of cellular and animal models that allow researchers to model the disease more accurately. In addition, the recent advances in high throughput drug screening allows for the efficient testing of patient-derived cardiomyocytes for patient-specific susceptibility to various drugs that are currently approved. In addition, this technology can facilitate the development of new pharmacological compounds for the treatment of specific cardiomyopathies. Overall, the recent technological advances in molecular medicine now presents an opportunity to gain unprecedented insight into solving the complex issue of inherited cardiomyopathies. These techniques pave the way for the new generation of personalized medicine in treating cardiovascular diseases.

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Introduction

Inherited cardiomyopathies are forms of heart disease that have a strong genetic basis in the form of specific genetic mutations. These diseases have an onset in adolescence and they burden the patients and their families over the entire lifespan. There are several different degrees of inherited cardiomyopathies including hypertrophic, dilated, restrictive, and arrhythmogenic right ventricular cardiomyopathies, among others. These categories were established as diagnostic classifications to delineate proper treatment options, but even within these distinct categories there is significant heterogeneity in terms of patient genetics [1]. As a result, current treatment plans for patients with specific cardiomyopathies is often less than effective [2, 3]. Therefore, this review supports the role of genetic factors as the primary predictors of patient-specific cardiomyopathies and argues for using patient-derived induced pluripotent stem cells (iPSCs) and high-throughput pharmacogenomic screens to optimize treatment for cardiomyopathies.

Genetic Diversity in Patients with Cardiomyopathy

Over the years, the identification of genetic mutations in patients with various cardiomyopathies has greatly improved our ability to diagnose and treat the disease. This is because there is a strong correlation between specific mutations, like those in the cardiac myosin heavy chain gene, and specific cardiomyopathies (i.e., hypertrophic cardiomyopathies) [4]. Although there is little doubt that familial genetics contribute most to the incidence of cardiomyopathies, our ability to diagnose specific cases of cardiomyopathy is complicated by additional genetic, environmental, and phenotypic diversity amongst these patients. The phenotypic heterogeneity between patients is exemplified by incomplete penetrance, meaning not all patients with specific mutations display the phenotype to the same extent [1]. For example, patients with dilated cardiomyopathy due to mutations in the Lamin A/C (LMNA) gene often show progressively declining cardiovascular function to varying extents [5], suggesting also that environmental factors (i.e., diet, lack of exercise) may contribute to the severity of disease symptoms that cannot be explained by just patient genetics [6].

What further complicates our understanding of cardiomyopathies is the genetic variation between patients that present with specific cardiomyopathies. For example, unique missense mutations have been detected in the same sarcomeric protein-encoding genes that lead to hypertrophic or dilated cardiomyopathies, which have very different physiological consequences [7]. On the other hand, there are also cardiomyopathies such as those caused by PRKAG2 mutations and Fabry’s and Danon’s disease, which are phenotypically similar to hypertrophic cardiomyopathy but have a different genetic basis [1]. In summary, identifying specific genetic mutations in cardiomyopathies have facilitated clinical diagnosis and improved treatment plans for patients with different cardiomyopathies. However, the genotype-phenotype correlation is far from perfect, suggesting that treatments designed to targeted groups of patients with a specific kind of cardiomyopathy is unlikely to be effective.

Targeting Patient-Specific Cardiomyopathies

It is our belief that the most novel and promising developments for the study and treatment of cardiomyopathies come from our improved ability to model these diseases in a patient-specific manner using iPSC technology and high-throughput drug screening. Recent developments in cardiac reprogramming allow researchers to take patient fibroblasts and reprogram these cells into iPSCs that can then be differentiated into cardiomyocytes to study specific disease mechanisms that underlie patient-specific cardiomyopathies [8]. This approach has been made even simpler with the development in gene editing technology using CRISPR-Cas9, as specific point mutations can now be made in wild-type iPSC-derived cardiomyocytes in a matter of days [9], which allows for pathway analysis to be done very quickly in cells that model any known mutations seen in patients. Using this approach, disease-contributing factors at the epigenetic level have been identified. For example, in an iPSC model of dilated cardiomyopathy with a mutation in the TNNT2 protein, it was found that phosphodiesterases (PDE) contribute to the disease and that the upregulation of PDE occurs as a result of decreases in a repressive histone modification (H3K27me3) at enhancers of PDE genes [10]. Studies such as this have contributed to the recent advances in our elucidation of aberrant signalling pathways in patients with specific cardiomyopathies. Using this system will allow us to better understand the discrepancies between the genotype and phenotype of certain cardiomyopathies through the identification of differences in the epigenetic markers and cellular pathways utilized. Therefore, in addition to diagnosing patients with specific cardiomyopathies via the identification of
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Moreover, it is believed that another promising new approach to treating cardiomyopathies in a patient-specific manner is to combine iPSC-derived cardiomyocytes that model specific mutations seen in patients and high-throughput drug screening approaches to test the efficacy and toxicity of pharmaceuticals. This combinatorial approach has led to the identification of genetic mutations that make certain patients more susceptible to cardiomyopathy when undergoing cancer treatment with the drug doxorubicin [9]. In another example, this pharmacogenomic approach has led to clinical trials that include incorporating polymorphisms in cytochrome P450 genes to optimize warfarin dosing [11]. Therefore, this approach is being used to optimize the delivery and facilitate the screening of drugs being tested for cardiomyopathies. Pharmaceutical companies are also using this approach with larger compound libraries and a larger pool of patient-derived cells to facilitate the development of new drugs to treat cardiomyopathies [12]. Therefore, using pharmacogenomics allows us to optimize benefit and minimize potential harm to individual patients. Utilizing this kind of approach will allow clinicians and researchers to get closer to fulfilling the promise of personalized medicine by providing patient-specific care and treatment for their unique cardiomyopathy.

Conclusion

In the past 20 years, the evolution of sequencing technologies has led to the identification of numerous genetic mutations that have contributed significantly to the diagnosis of inherent cardiomyopathies. However, these screens on individual patients also revealed issues such as incomplete penetrance, genetic heterogeneity, and a poor genotype-phenotype correlation that cannot be solved by studying the disease on a purely genetic level. Recent advances in cellular reprogramming technologies have allowed for the elucidation of dysfunctional epigenetic and cell signalling pathways in patient-specific cardiomyopathies. However, even with our improving understanding of the disease, the gap between knowledge and clinical translation remains. It can be argued that the most promising therapeutic approach is one that combines high-throughput drug screening with patient-specific models, with pharmacogenomics being one example of this approach.

Disclosure Statement

The authors declare no conflict of interest.