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Hypertrophic Cardiomyopathy: An Evolutionary Approach

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Abstract

Hypertrophic cardiomyopathy (HCM) is a genetic disorder that is characterized by left ventricular hypertrophy unexplained by secondary causes, and a non-dilated left ventricle with preserved or increased ejection fraction. It is commonly asymmetric with the most severe hypertrophy involving the basal interventricular septum. Left ventricular outflow tract obstruction is present at rest in about one third of the patients, and can be provoked in another third. The histologic features of HCM include myocyte hypertrophy and disarray, as well as interstitial fibrosis. The hypertrophy is also frequently associated with left ventricular diastolic dysfunction.

Keywords: Cardiac hypertrophy; genetics; human; mutation; sudden cardiac death; heart failure

Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic disorder of cardiac myocytes that is characterized by cardiac hypertrophy, unexplained by the loading conditions, a non-dilated left ventricle and a normal or increased ejection fraction. Cardiac hypertrophy is usually asymmetric with greatest involvement most commonly of the basal interventricular septum subjacent to the aortic valve. It is occasionally restricted to other myocardial regions, such as the apex, the mid-portion as well as the posterior wall of the left ventricle. At the cellular level, cardiac myocytes are hypertrophied, disorganized, and separated by areas of interstitial fibrosis. Cardiac hypertrophy may be of late onset, and less than 13 mm, the diagnostic cut point for the diagnosis of HCM. Hence, HCM may be under-diagnosed in such individuals. Conversely, cardiac hypertrophy could result from the phenocopy conditions (see below), which might account for 5 to 10% of the clinically diagnosed HCM cases in children. Moreover, the presence of concomitant conditions which may cause myocardial hypertrophy, such as arterial hypertension or aortic stenosis, may make the differentiation of primary (HCM) from secondary hypertrophy challenging. However, the asymmetric shape of the ventricle with greatest hypertrophy of the basal interventricular septum and genetic testing of the subjects and their families (see below) may be helpful in this population.

Pathogenesis

Gene mutation is the initiating pathogenesis of HCM affecting the proteins by playing a critical role in the function of the cardiac muscle unit "sarcomeres." The function of the sarcomere may weaken due to an abnormality in or shortage of any one of these proteins, which, in turn, affects the normal myocardial contractility. It is still not exactly described how the mutations in the sarcomere-related genes cause hypertrophy of the heart muscle

(1) Mutations in the sarcomere-related genes are associated with an increased affinity for calcium in the myofilaments, activate the calmodulin kinase II (CaMKII) pathway, and delay the downstream targets of the CaMKII sodium channels, thus increase the intracellular calcium and, thus, forming a vicious cycle. This results in the impaired relaxation and diastolic dysfunction of the myocardium.

(2) Mutations in the sarcomere-related genes in HCM can lead to inefficient contractility with a resultant increase in the ATP demand. This impairs the structure and function of the mitochondria leading to energy supply disorders. Microvascular dysfunction further exacerbates the myocardial energy deficiency of HCM and restricts the transport of the oxidative metabolites. The imbalance between the energy supply and demand leads to the myocardial cells in a state of peroxidation and then produces various reactive oxygen species (ROS), resulting in the glutathione acylation of the muscle filaments [cardiac myosin-binding protein C (cMyBP-C)]. Functionally, this modification increases the myofilament calcium sensitivity and inhibits the kinetics of cross-bridge cycling, leading to the diastolic dysfunction and ultimately aggravating the HCM phenotype.

(3) Due to the mutations in the sarcomere-related genes, the accumulation of the harmful proteins results in a toxic effect on the myocardial contractile devices and myocardial cells.

(4) Sarcomeric protein transcription and posttranslational modifications, as well as the other modified genes, also promote the development of HCM. Studies have shown that polymorphism of angiotensin I can contribute to the hypertrophic phenotype. These modified factors stimulate non-cardiac cell proliferation such as fibroblasts, thereby promoting the development of HCM. In conclusion, the functional changes at the cellular and molecular levels could be target of innovative therapies.

Novel Therapies

Calcium Desensitizer

Ca^{2+} overload, CaMKII, and increased I_{NaL} play a very important role that drive the myocardial remodeling from the earliest stage of the development of hypertrophy, diastolic dysfunction, and the arrhythmogenic substrate.

Blebbistatin

Blebbistatin is an inhibitor of actin-myosin interaction functioning independently of Ca^{2+} influx . Studies have shown that blebbistatin, in a mouse model of HCM caused by troponin T mutation, can reduce the sensitivity of Ca^{2+} to myofilaments and the incidence of arrhythmias; meanwhile, several studies Grillo et al. also reported that reducing the sensitivity of Ca^{2+} to myofilaments can be a target for the HCM treatment.

Metabolic Regulation-Energy Expenditure Hypothesis

In HCM, the mutations in the sarcomere gene result in reduced contractile efficiency of the sarcomere and an increase in ATP consumption. The characteristic of the HCM substrate metabolism is the preferential use of fatty acid (FA) oxidation, but in order to adapt to the consumption of more ATP, energy metabolism transfers to glucose metabolism to produce more ATP.

Diagnosis

The diagnosis of HCM rests on the detection of increased LV wall thickness by any imaging modality in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy.

In an adult, HCM is usually recognized by maximal LV wall thickness ≥ 15 mm, with wall thickness of 13 to 14 mm considered borderline, as measured by any imaging technique (echocardiography or cardiac magnetic resonance imaging), particularly in the presence of other compelling information (e.g., family history of HCM.

Conclusion

Since its modern characterization more than a half century ago, progress in the diagnosis and management of patients with HCM has paralleled technological advances in genetic testing, cardiac imaging, prevention of serious arrhythmias, cardiac surgery and interventional cardiology, Enhanced annotation of the human genetic variants and their variable relation to clinical expression is likely to facilitate identification of persons who carry the pathogenic variants. It is anticipated that in the future the field will shift from targeting phenotypes such as myocyte hypertrophy, fibrosis, arrhythmias and LVOT obstruction, toward correcting the underlying genetic disorders.

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