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NANOTECHNOLOGIES AND NANOSCIENCES, KNOWLEDGE-BASED MULTIFUNCTIONAL MATERIALS, AND NEW PRODUCTION PROCESSES AND DEVICES

CATALOGUE OF POSTERS

4.8 Take a Walk on the Nano Side: Structural and Energetical Analysis of ATP-binding Pocket Mutations of the Cardiac Beta-Myosin Heavy Chain Implicated in Familial Hypertrophic Cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is clinically defined by the presence of a hypertrophic, nondilated left ventricle in the absence of an increased external load, and pathologically by myocyte hypertrophy, disarray, and interstitial fibrosis.

The clinical outcomes of HCM are highly variable, and range from asymptomatic benign course to hearth failure or sudden cardiac death (SCD). HCM is inherited as an autosomal dominant trait; approximately 2/3 of the patients have a family history of HCM or SCD, while in the reminder of sporadic cases the causing mutations arise de novo. During the last decades, more than 100 different mutations in 10 genes encoding contractile sarcomeric proteins have been identified in patients with HCM, the locus of the β-myosin heavy chain gene (β-MyHC) on chromosome 14q1 being firstly identified as a responsible gene for HCM. The gene is comprised of 40 exons, and codes for a 6kb mRNA and a 220 kD protein (β-myosin heavy chain). It is the predominant myosin isoform in the ventricle of large rodents and humans, including more that 90% of the total myosin in the human ventricles.

Mutations in the β-MyHC are the most common causes of HCM and account for approximately 35-50% of all HCM cases. Thus far, over 60 different mutations have been described, the majority of which are β-myosin heavy chain missense mutations located within the globular head of the myosin molecule. This raises the challenging question of how molecular defects in contractile proteins can lead to disorganized myocytes and myofibrillar disarray, hypertrophy of the left ventricle, and an increased probability of premature death.

The localized preponderance of β-myosin mutations suggests that alterations in the motor activity of myosin may be more likely to provoke HCM than mutations on the β-helical rod. Further, most in vitro studies have concluded that specific HCM mutations cause a loss of function in the biochemical and mechanical properties on myosin. Hypertrophy would then follow as a compensatory mechanism to raise the work and power output of the failing hearth. All these assertions, although well supported by biochemical evidences, are not supported by any investigation at the computational biology level. Accordingly, we present the results obtained from a detailed molecular simulation study of wild type and mutated β-myosin heavy chains T124I, Y162C, V186L, N187K, N232S, and F244L, all belonging to the ATP-binding pocket and found involved in HCM, aiming at offering, for the first time, both a qualitative and a quantitative picture of the molecular mechanism at the base of F-HCM. The major purpose of this work is to propose a reliable and relatively fast computational recipe for the classification of different mutations in the domain with enzymatic activity of myosin towards HCM. This technique could be adopted as a routine analysis and could concur to throw a new light on the knowledge of this complex disease.