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Chromatin Compaction in Noncompaction Cardiomyopathy

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Noncompaction cardiomyopathy (NCM) is among a recently recognized cardiomyopathy with a distinct “spongy” appearance to the myocardial wall. It was first described in 1984[1] in the context of congenital heart disease and not recognized as an independent form of cardiomyopathy for another 50 years until Chin *et al.* first reported a cohort of isolated NCM[2]. The characteristic feature of NCM is heart failure, with imaging studies demonstrating a two-layered ventricular wall with a thin outer layer of compact myocardium and a deep, sponge-like inner layer of trabecular myocardium. While the left ventricle is the most predominant form, the right ventricle is increasingly understood to have a similar role. However, despite advanced imaging techniques, it is still challenging to differentiate normal left ventricular trabeculation versus NCM or the relationship of trabeculation in other more common forms of cardiomyopathies, including dilated and hypertrophic. As a result, the reported prevalence of NCM varies considerably across studies, likely reflecting heterogeneous populations, inconsistent clinical criteria, and diagnostic challenges in imaging. Indeed, less than half of NCM cases are felt to be genetic, with the remaining half sporadic or with no clear mutation[3].

Clinically, the symptoms vary significantly from asymptomatic adults to severely affected congenital patients. The most common presenting symptom is heart failure. In the most severe form, patients develop heart failure, arrhythmias, and sudden cardiac death[4]. The diagnosis of NCM is typically made on echocardiography, where multiple groups have reported similar, though variable, diagnostic criteria. Most studies show two layered myocardium with a hypoplastic (thin) outer compacted layer lined by the epicardium and a hyperplastic (thick) inner layer with prominent trabeculations lined by the endocardium. Additionally, with color flow doppler, there must be evidence of blood flow within the deep trabecular recesses[5]. Cardiac MRI is an emerging modality with high diagnostic sensitivity

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Disclosures

None

and is becoming the gold standard for NCM diagnosis.[5] The prevalence of noncompaction, particularly left ventricular noncompaction, ranges from 1.28% by cardiac echography and 14.79% by cardiac MRI in the general population or 0.9% and 9.76% in cardiac cohorts, respectively[6]. The cardiac MRI cohort likely overrepresents the prevalence due to a higher pretest probability for patients who need a cardiac MRI. In contrast, the prevalence could be lower in the echocardiography cohort, given that many patients are asymptomatic and may not undergo cardiac imaging.

An additional challenge in diagnosing and understanding NCM is the difficulty in correlating genotype and phenotype. While several known mutations can lead to NCM, including sarcomere proteins MYH7, MYBPC3, and TTN[3], the relationship between defective gene function and clinical phenotype is unclear. Interestingly, the involvement of primarily sarcomere proteins suggests that mutations within the cardiomyocytes may play a role in NCM. However, the same genetic mutation is associated with a large variation in clinical presentation, making prognosis and management strategies challenging. Reflective of this, there is a lack of cohesive understanding of where NCM fits within the clinical milieu of cardiology: the World Health Organization and American Heart Association, for example, have classified NCM within the genetic cardiomyopathies. At the same time, the European Society of Cardiology has left it unclassified, given ambiguity as to whether NCM is a distinct cardiomyopathy or a trait of several other cardiomyopathies. Additionally, noncompaction cardiomyopathies are identified in several forms, including isolated, arrhythmogenic, dilated, hypertrophic, biventricular, right ventricular hypertrabeculation with the normal left ventricle, associated with congenital heart disease and, the most common, left ventricular form (LVNC)[4]. Current treatments of NCM primarily focus on the sequelae of the disease, with goal-directed medical therapy for heart failure or ICD placement for arrhythmia. So far, no treatments focus on the disease process itself. Additionally, given the diagnostic ambiguity and clinical variability, there is a need for a deeper understanding of the genetics of trabeculation and noncompaction.

A recent exome sequencing of a cohort of 2,871 congenital heart disease probands identified 46 chromatin-modifying genes with deleterious de novo mutation, including chromodomain helicase DNA binding protein 4 (CHD4), a component of the Nucleosome Remodeling and Deacetylase (NuRD) complex[7]. In this edition of *Circulation Research*, Shi *et al.* characterize a newly identified human CHD4 genetic mutation in mice to aid our understanding of the NCM disease process[8]. The authors proposed that given the association of ventricular chamber development with chromatin structure as a regulatory process of cardiac gene expression programs, mutations in the chromatin modeling complexes may play a role in NCM. NuRD is the most studied, evolutionarily conserved, multisubunit chromatin complex that functions as a master regulator of genetic programs in development and disease[9]. The complex is composed of chromatin remodelers CHD3/4/5, histone deacetylases 1/2 (HDAC1/2), and non-enzymatic components including MDB2/3, RBB4/7, MTA1/2/3, GATAD2A/B[10]. While initially felt to be a repressive complex,[9] recent work has shown that it can function as an activator as well[11]. The complex is strongly associated with congenital heart disease[12], and CHD4, the core catalytic component of the complex, has been shown to regulate cardiac development and function[13]. We have previously shown

that mice lacking Hdac1/2 or Hdac3, class I histone deacetylases, exhibit NCM and cardiac developmental defects[14, 15].

To better understand the role that CHD4 plays in human congenital heart disease, the authors screened the complete exome sequence database of the Pediatrics Cardiac Genomic Consortium[16] to identify a *de novo* CHD4 proband cohort with congenital heart disease associated with a CHD4^{M202I} missense mutation. Interestingly, while the proband was associated with ventricular septal defects and conotruncal abnormalities and not NCM when the missense mutation (CHD4^{M195I}) was introduced in a mouse, the homozygous mice (CHD4$^{M195I/M195I}$) exhibited LVNC. The heterozygous form showed no significant abnormalities; however, the homozygous mutation led to a complete neonatal lethality, and the heart showed a dramatically reduced ventricular cavity with an increase in the trabeculation, consistent with LVNC.

The authors examined the development of the phenotype and found a thinner compact layer at embryonic day 12.5 (E12.5), thicker trabeculations at E14.5, and a failure of trabeculation folding at E16.5 in CHD4$^{M195I/M195I}$ hearts. These observations persisted to birth and suggested that trabeculation was a dynamic remodeling process that failed in the CHD4^{M195I} global knockout mice. Further investigation showed that the knockout hearts exhibited hyperproliferation of immature cardiomyocytes in the trabecular layer compared to the wild-type controls. The CHD4^{M195I} homozygous mutation also led to dysregulation of extracellular matrix remodeling programs, most notably Adamts1, a known matrix metalloproteinase that has been shown to aid termination of trabeculation, thus compaction[17]. CHD4^{M195I} frequently recruited Brg1 to the chromatin, likely repressing *Adamts1* expression and resulting accumulation of extracellular matrix during cardiac development. The recombinant Adamts1 protein administration attenuated key aspects of the LVNC phenotype, including hypertrabeculation, although the thinning of the compact layer did not improve.

The insights into LVNC pathogenesis are significant. The work suggests that trabeculation is a highly dynamic process driven by the maturation of the developing cardiomyocytes and decreased cell proliferation. The extracellular matrix also appears to be a key component of the developmental process. Further, the partial rescue of the phenotype with recombinant Adamst1 suggests that spatial regulation is also highly controlled in addition to the temporal regulation of myocardial compaction. The mouse study by *Shi et al.* was a global missense CHD4^{M195I} mutation. Most cases of NCM are sporadic and do not appear to be germline, suggesting that the disease process is likely driven by somatic mutations in a cell-specific manner. A hallmark of chromatin dynamics, particularly development, is the temporal and spatial specificity of chromatin remodeling[18]. As a result, future work may enhance the clinical translatability of the model by studying cell-specific or, as the paper notes, conditional mutants. This would enable spatiotemporal control of CHD4^{M195I} missense mutation and likely be most reflective of the clinical condition. The global missense mutation noted in this study versus the likely somatic mutations in the proband, and species difference is likely reasons the phenotype varied between the proband and the humanized CHD4$^{M195I/M195I}$ mouse. Enhancing our understanding of the trabeculation process and where this process fails in NCM is essential for future therapeutic development, risk

stratification, and diagnosis. Identifying CHD4^{M202I} – and the importance of chromatin dynamics in general – as a key regulator of trabecular development and NCM represents a significant step forward in our understanding of this disease.

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