

Review

Formation and Malformation of Cardiac Trabeculae: Biological Basis, Clinical Significance, and Special Yield of Magnetic Resonance Imaging in Assessment

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ABSTRACT

Adult and pediatric cardiologists are familiar with variation in cardiac trabeculation. Abnormal trabeculation is a key feature of left ventricular noncompaction, but it is also common in congenital heart diseases and in cardiomyopathies (dilated and hypertrophied). Trabeculae might be a measurable phenotypic marker that will allow insights into how cardiomyopathy and congenital heart disease arise and develop. This will require the linking together of clinical and preclinical information (such as embryology and genetics), with new analysis methods for trabecular quantitation. In adult cardiology several promising quantitative methods have been developed for echocardiography, computed tomography, and cardiovascular magnetic resonance, and earlier cross-sectional caliper approaches have now been refined to permit more advanced assessment. Adaptation of these methods for use in developmental biology might inform on better ways to measure and track trabecular morphology in model organisms.

RÉSUMÉ

Les trabéculations cardiaques, tant chez l'enfant que chez l'adulte, sont un phénomène bien connu des cardiologues. En effet, la présence de trabéculations anormales est l'une des caractéristiques clés de la non-compaction ventriculaire gauche, mais se retrouve aussi dans de nombreuses cardiopathies congénitales et cardiomyopathies (dilatation/hypertrophie du cœur). Les trabéculations pourraient constituer des marqueurs mesurables du phénotype et offrir ainsi une perspective intéressante sur l'apparition et l'évolution des cardiopathies congénitales et des cardiomyopathies. Pour ce faire, il faudra cependant faire le lien entre les données cliniques et précliniques (d'embryologie et de génétique) et les nouvelles méthodes d'analyse pour quantifier les trabéculations. Chez l'adulte, les cardiologues ont mis au point de nombreuses méthodes de quantification prometteuses à l'aide d'imagerie par échocardiographie, de tomographie et de résonance magnétique, et les anciennes approches de mesure d'images en coupes transversales ont été revues de manière à permettre une évaluation plus précise. L'adaptation de ces méthodes pour qu'elles puissent être utilisées dans le cadre de la biologie du développement pourrait nous aiguiller sur des façons de mieux mesurer et suivre l'évolution de la morphologie des trabéculations chez des modèles expérimentaux.

In this review we outline the biological significance of myocardial trabeculae and their effect on normal cardiac development. The heterogeneous spectrum of trabecular complexity in the general population is emphasized and a clinically useful algorithm to guide the management of patients discovered to have abnormal trabeculation at the time of cardiac imaging is suggested.

Biology and Clinical Relevance of Trabeculae

Myocardial trabeculae make their first embryonic appearance in the developing mouse at the end of cardiac looping, specifically at embryonic days (E) 9.0–9.5 (Carnegie stage 12 in the human). An early role is believed to be that of optimization of efficient nutrient and gas exchanges before the development of the coronary arteries¹ (the mouse heart is devoid of any intramural vessels until E12.5²). By E14.5 (Carnegie stage 22 in the human) ventricular septation is complete and a dense trabecular meshwork is established within the ventricular cavities.³ This decreases by the time of birth with the formation of papillary muscles, the moderator band, and effective arterial valves in a functioning adult patterned heart. Morphologically, 2 sequential phases of trabecular development can be identified in the mouse (Fig. 1): (1) an early phase (E9.0–13.5) dominated by

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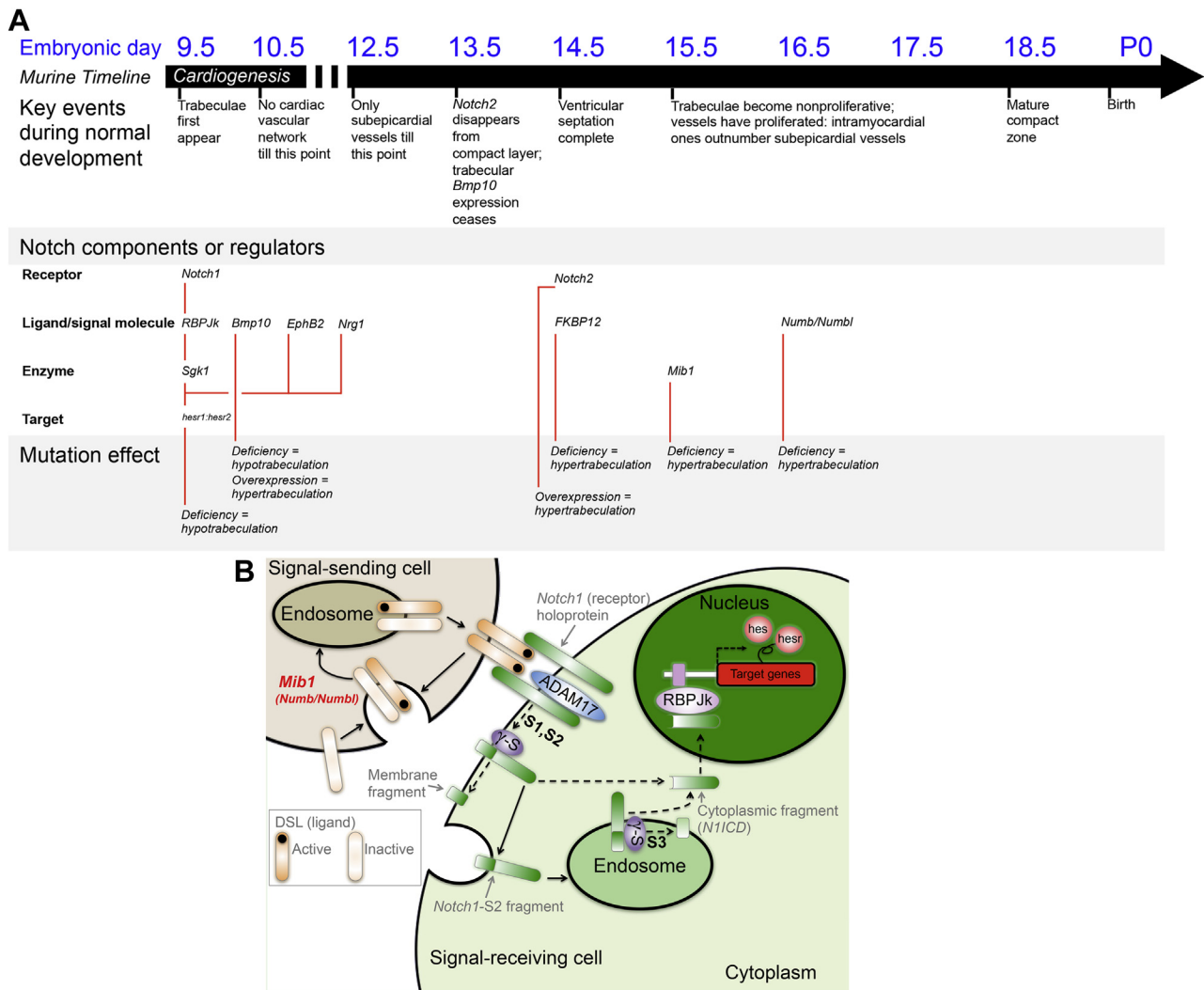


Figure 1. (A) Sequential morphological phases of trabecular development in the mouse are governed by a complex number of signalling pathways and trophic factors. As an example, this figure is focused on the Notch signalling pathway (**bottom**) for its role in the cause of aberrant trabecular phenotypes in mutants. Key developmental stages in the embryonic mouse heart (**black horizontal timeline arrow**) are shown above. **(B)** Notch is 1 of several signalling pathways that influence trabecular development. Notch converts information about the concentration of extracellular ligands into specific transcriptional responses in the nucleus. In mammals, Notch comprises 2 groups of transmembrane proteins: (1) 4 receptors (*Notch1*, 2, 3, and 4); and (2) 5 ligands (that contain a *Delta/Serrate/Lag2* motif in their extracellular domain). *Notch1* receptor-ligand interaction results in a series of cleavage events (S1, S2, S3) that affect the receptor holoprotein. Cleavage of the Notch extracellular domain by ADAM metalloproteinase domain 17 is followed by cleavage of the intracellular portion by a γ -secretase that releases the Notch intracellular domain into the cytoplasm. From there, Notch intracellular domain translocates to the nucleus where it forms a complex with the recombination signal binding protein for immunoglobulin kappa J region (*RBPJk*, a transcription factor) and other coactivators to transactivate transcription of downstream target genes like the hairy and enhancer of split (*hes*) family genes and the *hes-related* (*hesr*) family genes (also known as the *hrt/hey/herp* family genes).^{4,5} *Notch1* activation in the developing trabeculae has recently been shown to depend on ubiquitination and endocytosis of ligands *Delta* and *Jagged* by the E3 ubiquitin ligase mindbomb homolog 1 (*Mib1*), shown in **red**. ADAM, A disintegrin and metalloprotease; *Bmp*, bone morphogenetic protein; *EphB*, ephrin-B; *FKBP12*, FK506 binding protein-12; *Nrg1*, neuregulin-1; S, cleavage site/s; *Sgk1*, serum and glucocorticoid-inducible kinase 1; P0, postnatal day 0 (birth).

the formation of a thick trabeculated meshwork, mediated through cardiomyocyte differentiation and terminal proliferation, and maintained by intact ligand/receptor interactions between endocardial cells and between endocardial and myocardial cells⁶ (Fig. 2); and (2) a late phase (beyond E13.5) in which the trabecular zone is less dense and a thick compacted layer is observed. The commonly held view that trabeculae in this late phase of cardiac development “condense” somehow to give the compact layer, leaving only a little behind (as seen in the adult human heart) is still lacking compelling evidence.

Further research is needed to definitively show how the 2 events of trabecular remodelling and compact layer formation in the developing heart are linked rather than distinct.

Using small animal models, genetic disruptions that affect the normal endo- and myocardial crosstalk in the developing heart have already been shown to manifest as either decreased or increased trabeculation (specific examples are listed in Table 1). Notably, hypotrabeculated mutants exhibit severe heart failure and embryonic lethality indicating that trabeculae have a ‘prosurvival’ role in cardiogenesis. Trabecular

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