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TOPICAL REVIEW

Rhythms of growth: unveiling the mechanobiology behind heart maturation

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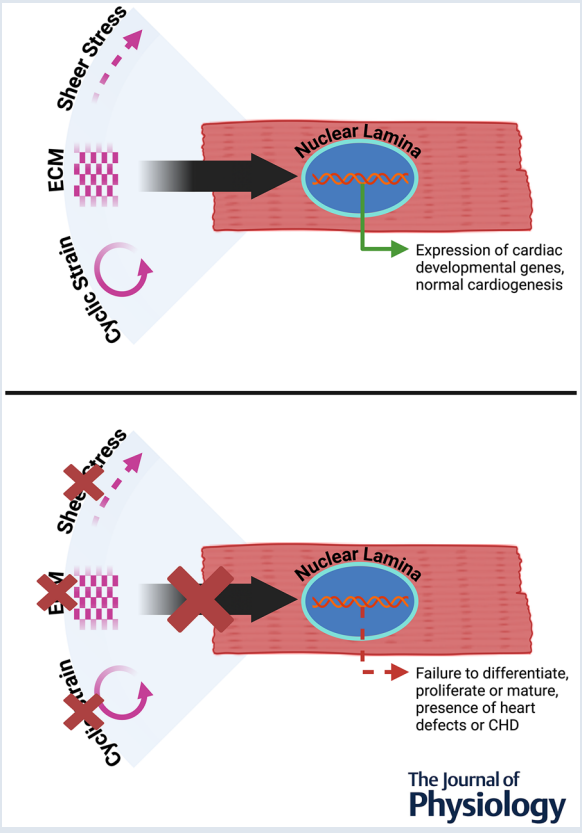

Abstract figure legend Effects of mechanical stimuli – shear stress, ECM components and stiffness, and the contractility – in the nuclear lamina during cellular development of the heart. Mechanotransduction events that play a role in the proliferation, differentiation, and maturation of cardiac development are likely to be associated with the underlying nuclear lamina, which mediates interactions with transcription factors and chromatin domains to regulate gene expression throughout cardiac development. Top image: Mechanotransduction effects influence the activation of genes during cardiogenesis, promoting the growth of the heart. Bottom image: Lack of mechanical stress leads to cellular failure to promote differentiation, proliferation or maturation, resulting in heart defects and congenital heart disease (CHD).

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Abstract The physiological function of the heart depends on highly coordinated cellular communication, especially during cardiogenesis, when changes in blood flow, extracellular matrix components, and contraction actively drive chamber remodelling. These changes are modulated by cellular behaviour to establish growth for cardiac developmental structure and function. One key to these processes is mechanotransduction, which is the ability of cells to sense and respond to mechanical stimuli. Mechanical cues influence the dynamic expression of genes at each embryonic stage, which plays a critical role in regulating cell migration, differentiation, proliferation, and maturation. In this review, we correlate the mechanobiology of the growing heart with the ability of the nucleus to sense mechanical strain and thereby influence gene expression and cell fate. We examine established roles of signalling pathways and gene expression changes during heart development, while highlighting gaps in our understanding of these complex processes. Considering the mechanosensitive effects of nuclear proteins in translating complex instructions to the nuclear lamina, thereby influencing chromatin states and transcription factor activity, we propose that the exploration of nuclear lamina interactions on chromatin regulation during cardiogenesis holds great potential to drive groundbreaking advances in cardiac research. Thus, the study of mechanotransduction during cardiogenesis may provide a deeper understanding of the transcriptional mechanisms underlying heart formation, including insights into both regeneration and maturation processes.

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Introduction

Effective cellular communication is necessary to maintain physiological function, especially in a highly dynamic organ such as the heart. As the heart undergoes morphogenesis, changes in blood flow and contraction support chamber remodelling patterns and alter cellular behaviour to achieve the correct morphology and circulatory state. These changes are driven by many orchestrated processes, including the mechanotransduction effects of physical load in the heart. Mechanotransduction is characterized by the ability of cells to sense and respond to mechanical stimuli and can interfere with cell migration, differentiation, proliferation, maturation, and even gene expression. Thus, it grants distinct cardiac cell populations the ability to determine their own cellular fate, thereby defining their cardiac function. Despite the importance of mechanotransduction in cardiac development and maturation, its effects and underlying mechanisms remain poorly understood. In this review, we categorize the mechanical burden in the heart into three distinct forces: extracellular matrix (ECM) stiffness, shear stress, and contractility.

During cardiogenesis, appropriate dynamic-mechanical properties are achieved through a refined balance between fibroblasts and cardiomyocytes, creating a precise ratio for the contractile ability and ECM mass (Majkut et al., 2014). Derived from epicardium and endocardial layers, cardiac fibroblasts initiate the deposition of a collagenous matrix, which contributes to cellular differentiation, providing a structural role and supportive strength to cardiomyocytes (Souders et al., 2009). Additionally, the ECM components sustain the cardiac microenvironment by limiting cell behaviour, volume, and shape (Saraswathibhatla et al., 2023). As the heart grows, contractility gradually increases as the expression of contractile proteins occurs in temporal relation to cardiac performance. In a well-coordinated manner, contraction and relaxation are driven by electrical signals that actively generate force and strain in the myocardium. As a result

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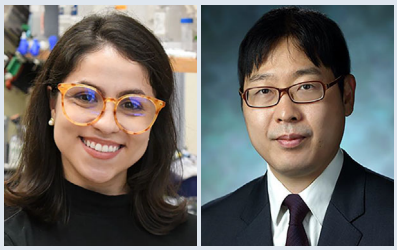

of the initial contractility during the formation of the cardiac tube and the growth of the ECM components, the stiffness of the heart increases during the maturation phase (del Monte-Nieto et al., 2020). Additionally, haemodynamics and shear stress play a critical role in heart morphogenesis and maturation. As the heart continues to mature, the pressure load and the blood flow increase, and the heart has to cope with these increasing forces. This biomechanical strain influences cardiac growth, anatomical organization, chamber formation and cell differentiation (Heallen et al., 2020).

These mechanical forces are transmitted intracellularly and by cell-cell communication, and are directly associated with the elastic properties of the ECM compliance (Emig et al., 2021). The ECM serves as a dynamic spatiotemporal regulator of cellular behaviour, modulating signalling pathways that influence processes such as cell migration, progenitor self-renewal, and cellular differentiation toward the organization of the anatomical four-chamber heart. In general, as mechanical strain on the heart –stemming from shear stress, pressure, and contractility – increases, the myocardium becomes increasingly organized and interconnected (Gaetani et al., 2020; Silva et al., 2021). The relationship between pressure and volume in the developing heart is also influenced by ECM stiffness, as the pericardial pressure exerted on the developing cardiac walls promotes increased deposition of ECM components (Shabetai, 2004). In fact, pressure overload in the heart is associated with higher collagen production resulting in fibrosis, a hallmark of pathological conditions (Bradshaw et al., 2009; Schwartz et al., 1996).

Together, active and passive biomechanical forces (Fig. 1) contribute to myocardial development, which is a key determinant of cardiac performance and growth, gradually increasing the cardiac stiffness until full maturity. This strong mechanotransduction interplay drives critical transcriptional and spatiotemporal responses, which are essential for the maturation process during heart development (Silva et al., 2021). Nonetheless, there is little understanding of how mechanical forces interact with the developing cardiac environment to regulate gene expression. In this review, we briefly describe the basic concepts of physical load modulators and speculate on their functions in cardiogenesis. In addition, we delineate established points of the mechanosensitive machinery through cardiac development and maturation, and discuss how mechanotransduction triggers cell fate at the molecular level.

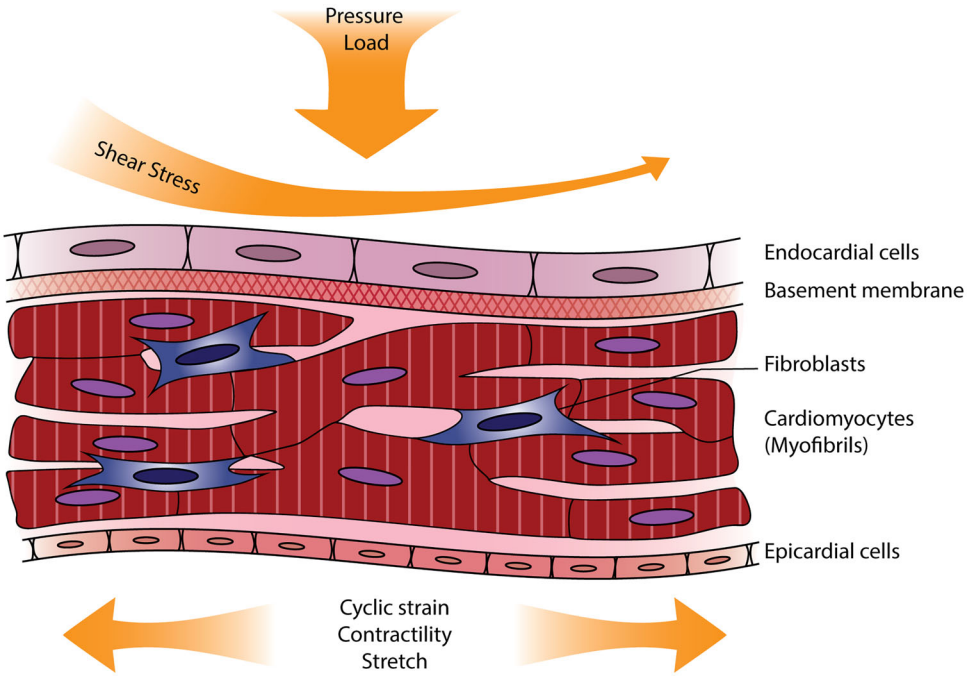

Figure 1. Mechanical forces in the myocardium
As components of haemodynamics, both pressure load and shear stress are directly sensed by endocardial cells. The basement membrane is rich in ECM components and separates the endocardial cells from the myofibrils, providing structural and mechanical support and anchoring points for the cells. Myofibrils are the source of contractile power and contain highly dynamic sarcomeres. Cardiomyocyte sarcomeres support cardiac function by generating the cyclic strain and stretch required to pump blood. Adjacent to the myofibrillar layer, epicardial cells are a progenitor source for numerous cellular populations and a physical barrier to the pericardial space.

Structure and intrinsic flexibility of the extracellular matrix and its major components

The mature cardiac ECM is composed of a complex mesh of proteins that assist signalling and structural organization, influencing cellular behaviour and tissue integrity. This matrix is the natural environment for cardiac myocytes, fibroblasts, leukocytes, and other cells of the myocardial vasculature (Hsieh et al., 2006). Predominantly composed of glycoproteins, glycosaminoglycans (GAGs), and proteoglycans; the ECM components are divided into two distinct categories: pericellular and interstitial. In adult myocardium, the most abundant fibrillar proteins (collagen I and III) are part of the interstitial matrix and provide structural and mechanical support. The pericellular matrix is composed of GAGs (e.g. hyaluronan), proteoglycans (e.g. perlecan, versican) and glycoproteins (e.g. fibronectin, laminin), which provide flexibility and promote cellular signalling and function. These ECM components are produced in specific regions and at specific times during cardiac development. A balanced composition of ECM components is critical for the maintenance of the cardiac microenvironment, as well as for the processes of development and maturation (del Monte-Nieto et al., 2020; Derrick & Noel, 2021).

Studies indicate that hyaluronan is specifically produced by endothelial cells (ECs) (Lagendijk et al., 2013), perlecan by both endothelial and smooth muscle cells (Gao et al., 2021), while versican, fibronectin, laminins, and collagen are predominantly produced by fibroblasts (Deng et al., 2024; Feng et al., 2024). However, recent findings demonstrate that cardiac progenitors also have the ability to synthesize ECM components, contributing to the matrix remodelling (Bax et al., 2012). The expression of these proteins increases under cardiac development and cell differentiation. In fact, as ECM components deposition increases, it promotes cyto-skeleton and myofibril alignment during myocardial maturation (Silva et al., 2021; Yahalom-Ronen et al., 2015). In functional myocytes, the contractile force closely corresponds to ECM stiffness (Engler et al., 2008), yet contraction cycles also influence matrix organization by cell-matrix interactions (Gupta & Grande-Allen, 2006).

Driven by the orchestrated expression of various proteins with distinct functions at different embryonic stages; the different subtypes of collagen, such as collagen I, III, IV, V, VI and XIV, play specific roles throughout developing stages. Collagen types I and III are found in increasing amounts as the cardiac ECM matures, and both types promote the fibrillar network growth, which provides structural integrity, strength and elasticity. An adult cardiac ECM can have a predominant abundance (38%) of collagen I, while fetal and neonatal cardiac ECM have only 11% and 16%, respectively (Williams et al., 2014). In mice, type III collagen is a major component in the prenatal stages of developing valves, but its ratio is reversed after birth and is mostly replaced by type I collagen (Falla Zuñiga et al., 2021). Changes in collagen I and III ratios can be correlated with the elastic capabilities of the cardiac wall during cardiogenesis. After proliferation and ventricular chamber formation, there is a decrease in compliance ability due to the diminished levels of collagen type III, resulting in an increased myocardial stiffness (Carver et al., 1991; Hall & Ogle, 2018). Similarly, in chick embryos, the total amount of collagen increases in response to the increased pressure and stress, contributing to chamber maturation (Jallerat & Feinberg, 2020).

Hyaluronan is a viscoelastic component of the ECM that is involved in the migration, transformation, and invasion of cardiac ECs, playing a major role in cardiac remodelling of cushions and valves. Studies show that knockout of the hyaluronan gene (*HAS2*) in mice displays lack of endothelial-to-mesenchymal transition (EndoMT), severe cardiovascular defects, and embryonic death (Camenisch et al., 2000). Embryonic expression of hyaluronan results in expansion of extracellular space and stimuli for ECs to transform and migrate, which are required steps for the formation of endocardial cushions (Camenisch et al., 2000, 2001). In addition, it has a salt- and water-attracting effect that helps binding molecules to the cardiac jelly, resulting in a strong network that supports the biomechanical effects of cardiac remodelling (Lagendijk et al., 2013).

Versican is a proteoglycan product derived from four alternative splice variants (*CSPG2* gene), of which the V0 and V1 isoforms are mainly expressed in the cardiac jelly of the cushions and leaflets during cardiogenesis, whereas the V2 isoform is observed in the myocardium and cardiac neural crest. It is known to promote cell proliferation, and loss of versican can lead to ventricular septal defects in mouse models, resulting in impaired cardiac looping, and absence of cardiac jelly (Feng et al., 2024). Once the heart is septated, versican is cleaved by proteoglycanase. This allows for development of fibrous structures and formation of the aortic and pulmonary valves (Dupuis et al., 2013). It is also associated with increased tissue rigidity and stiffness (Hirani et al., 2021). Another critical proteoglycan in extracellular matrix remodelling and physical support is perlecan, which is highly expressed during embryonic stages in mice and functions as a key player in the control of cellular population during formation of the outflow tract (Costell et al., 2002). Loss of the perlecan gene (*HSPG2*) causes severe leakage into the pericardial cavity and embryonic death, and also causes defective cell-cell communication, damage to ECM integrity, and myocardial infarction in adult hearts (Sasse et al., 2008). While perlecan is expressed at higher levels during early development in humans, its levels decrease as the ECM undergoes stabilization and maturation. This

may suggest that cardiac development requires high levels of perlecan for growth and proliferation, and as the heart transitions to a differentiated state and the composition of the ECM shifts, perlecan is no longer required (Johnson et al., 2024).

The increasing gradient of fibronectin in the cardiac crescent promotes the formation of the endoderm-mesoderm interface necessary for the formation of the heart tube. It acts as a bridge that allows cells to adhere to the abundant ECM network by regulating cell receptors and ECM proteins, and it mediates cell migration and cytoskeletal organization (Haack & Abdelilah-Seyfried, 2016). Human and zebrafish models show that fibronectin also mediates induction of precardiac mesoderm via promoting Wnt signalling during germ layer stages (Cheng et al., 2013; Uosaki et al., 2012) and is required for capillary formation and cardiomyocyte alignment during early vascularization in chick embryos (Jallerat & Feinberg, 2020). The absence of the fibronectin (*FN*) gene in mice can lead to severe cardiovascular defects and even arrested heart development (Astrof et al., 2007). Most abundant in fetal and neonatal hearts, fibronectin levels decrease to relatively low levels (approximately 4%) in adult cardiac ECM (Williams et al., 2014). This suggests that fibronectin may have a reduced role in adult heart tissue as the myocardium becomes stiffer and more stable, while contributing to greater flexibility and supporting cell fate during cardiogenesis.

Laminins are among the early ECM proteins present during heart development, locally expressed in the pericellular matrix. Laminin isoforms are differentially expressed and distributed during development, regulating key factors in cellular behaviour (Kruegel & Miosge, 2010). *In vitro* studies have demonstrated that laminin deposition increases in the heart, as other extracellular proteins are expressed, strengthening the fibrous ECM network between collagens and fibronectin (Schwach & Passier, 2019). During heart tube formation in rats, laminins localize to the cardiac jelly, expand their accumulation in fetal and neonatal hearts, and develop into a continuous layer in adult myocardium, comprising 14% of cardiac ECM (Williams et al., 2014). In addition to providing mechanical scaffolding, laminins support cell-cell interactions, modulate cell adhesion by interacting with integrins, dystroglycan and dystrophin, and contribute to growth factor interactions (Silva et al., 2021).

The synthesis and degradation of ECM components contribute to the dynamic nature of the cardiac ECM, which allows structural and biochemical changes to occur during development. The developing myocardium must withstand and adapt to changing pressures and organ growth, resisting increasing pressure overloads with active compliance, stretch and elasticity (Gaetani et al., 2020). As cells respond to increasing substrate stiffness, cell adhesion is strengthened by integrins, leading to the activation of signalling pathways that promote actin bundle assembly and actomyosin contractility in neonatal rat myocytes (Chopra et al., 2014). The ECM releases and activates matrix-bound growth factors (e.g. TGF-β, bone morphogenic proteins (BMPs), activins and nodal) as cellular traction force intensifies (Sorensen & van Berlo, 2020). In the downstream effects of the canonical and non-canonical TGF-β pathways, small molecules activate transcription genes such as *ERK*, *p38* and *JNK*, which participate in the mitogen-activated protein kinase (MAPK) signalling pathway and modulate cardiomyocyte proliferation. MAPK pathways are intrinsically linked to many cellular processes in human and animal models, including growth and proliferating cells, by activating genes such as *GATA4* and *Nkx2-5* (Wang, 2007). After birth, the ECM components and microenvironment change and cease to proliferate, and to compensate for the loss of regenerative properties, excessive accumulation of ECM leads to scarring and fibrosis with ageing, resulting in cardiac dysfunction (Silva et al., 2021). An elegant *in vitro* study has demonstrated the direct dependent relationship between ECM stiffness and gene expression by examining nuclear factor Y (NFY) in fibrotic adult myocardium (Ebrahimighaei et al., 2024). Stiffness and the extracellular environment influence several processes in cardiac development, where the composition of the ECM exerts major changes through its organization and mechanical adaptability.

The role of sarcomeric proteins in generating active force

Temporal changes in the expression of sarcomeric proteins are observed during heart development. While contractile function can be seen at approximately embryonic day (E) 8 in mice and 16 days post-fertilization in humans, calcium transients can be identified prior to the detection of the heartbeat (Tyser & Srinivas, 2020). The first demonstration of spontaneous calcium transients in embryonic hearts was found in the cardiac crescent of developing rats, which showed the exclusive involvement of Ca^{2+} entry through L-type calcium channels (Kobayashi et al., 2011). This is different from adult cardiomyocytes, which express a variety of excitation-contraction coupling (ECC) components to trigger contractile activity. Besides, before the pace of contraction and relaxation is established, the contractile machinery must be formed and organized along the early myofibrils (Sparrow & Schöck, 2009). The sarcomeric proteins are expressed in a time-dependent manner, with cardiac troponin T (cTnT) being one of the first to appear in the cardiac crescent, first visualized at low expression levels (Kobayashi et al., 2011). During cardiac crescent

folding, cTnT expression increases, whereas α-actinin and myomesin are detected after contractile function is initiated (Tyser et al., 2016; Tyser & Srinivas, 2020). Studies in various models of myofibrillogenesis indicate that the contractile force from the heartbeat is essential to the organization and maturation of myofibrils and the expression of sarcomeric proteins (Ichise et al., 2022; Sparrow & Schöck, 2009). Once the organization of the sarcomeric apparatus is achieved, the expression of other sarcomeric proteins increases throughout the embryonic cardiac tissue, resulting in improved Ca^{2+} handling and contractile rates. Furthermore, missing or impaired contractility during cardiogenesis is known to lead to diverse CHD phenotypes (Granados-Riveron & Brook, 2012).

The mechanical cues of contractile motion actively transmit forces into the ECM. Continuous exposure to mechanical force, sensed by cardiac cell populations, is associated with increasing tensile and compressive stress (Herum et al., 2017). As a result, heart tissue stiffness is elevated through increased expression of ECC proteins and contractile activity in the developing heart (Majkut et al., 2013). Studies demonstrate that optimal contractile activity, development, and positioning of sarcomeric proteins are associated with cardiac stiffening during cardiogenesis (Majkut et al., 2013, 2014). Also, expression of ECC proteins is not only sensitive to matrix mechanics (Gaetani et al., 2020), but also acts as a feedback force that drives the load on the elastic matrix, creating an optimal environment (Engler et al., 2008; Majkut et al., 2013). Heart stiffness levels start as low as 0.1 kPa and rising by 0.3 kPa per day in chick embryos (Majkut et al., 2013; Pesce et al., 2022). They reach 1–2 kPa at E12–E14 in mice (Münch & Abdelilah-Seyfried, 2021). The human myocardium can show stiffnesses of approximately 10 kPa at birth (Querceto et al., 2022) (Fig. 2), while beating activity can improve the myocardial environment both *in vivo* and *in vitro* (Gaetani et al., 2020; Herum et al., 2017; Majkut et al., 2013). Therefore, contractile activity leads to the physiological stiffness of the heart, which in turn plays a key role in the development and changes in protein expression.

It is only recently that cellular and molecular events during cardiogenesis have been linked to cardiomyocyte

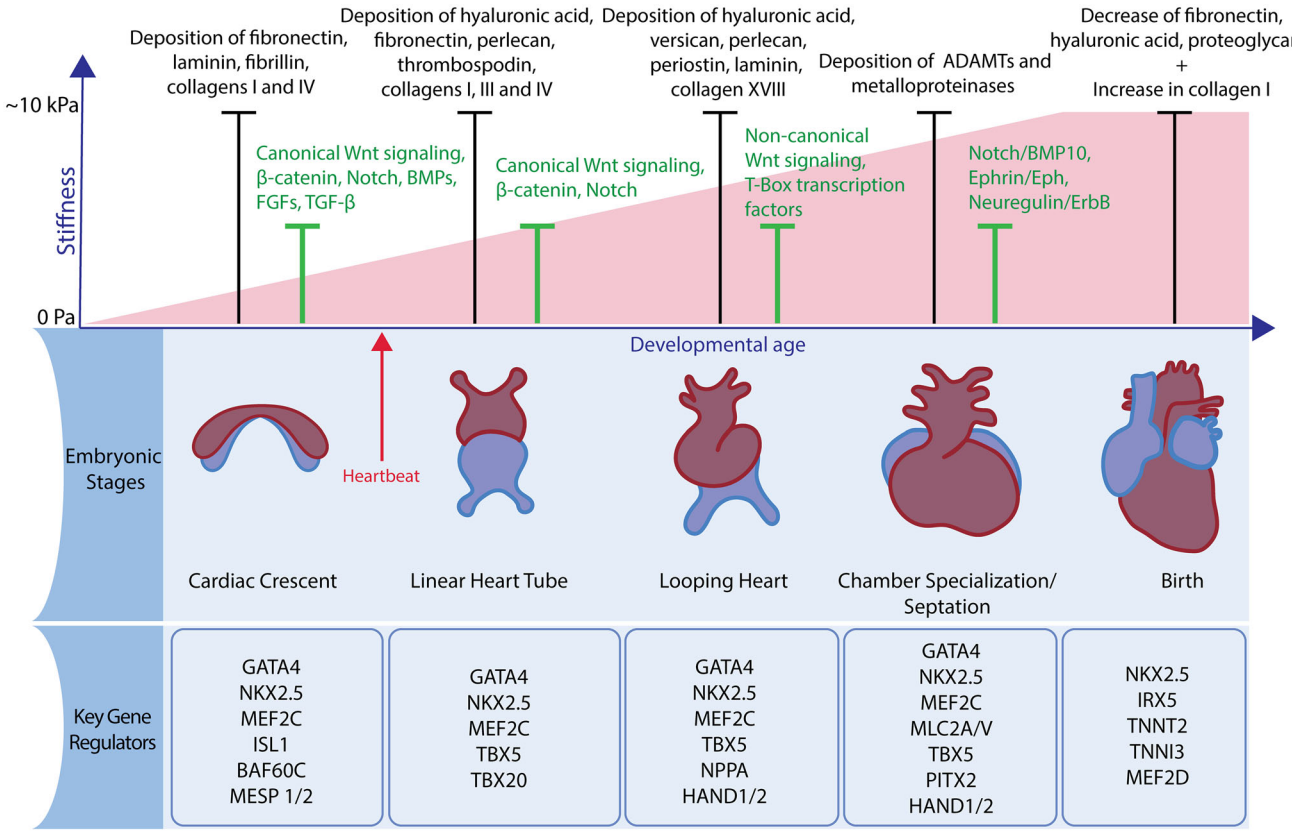

Figure 2. Developmental cardiac ECM deposition and tissue stiffness
Graph showing the increase in stiffness during the developmental stages of cardiogenesis (from 0 kPa to approximately 10 kPa). Increased stiffness is accompanied by differential deposition of ECM components and increased overall contractile force as the heart develops. Signalling pathways and transcription factors that regulate each embryonic stage are shown in green, with key genes that modulate remodelling events listed below.

contractility (Courchaine et al., 2018). A study showed that the gene *IDB2* – human homolog *ID2* – is particularly activated by the contractile rhythm. In the absence of contractile forces, *IDB2* expression is significantly reduced, resulting in cardiac malformation and embryonic death (Chen et al., 2024). In addition, EndoMT and activation of the Notch signalling pathway by Notch1b is initiated by both contractile force and flow stress in zebrafish studies (Samsa et al., 2015). As contractile activity increases during development, it contributes significantly to an expansion in the expression of ECC and sarcomeric proteins from cardiac-specific genes (Fukuda et al., 2019). For example, the cytosolic Ca^{+2} concentration must be dynamically regulated throughout the embryonic stages. In the early stages, the role of the sarcoplasmic reticulum (SR) is minimal (Tyser et al., 2016). However, as the heart develops and the sarcomeric machinery matures, the SR becomes essential for the contractile machinery, expressing functional RyR and IP_3Rs proteins that orchestrate synchronized Ca^{2+} release before the onset of contraction (Tyser & Srinivas, 2020). The overall force-generating capacity increases until adulthood, and it is closely associated with Ca^{2+} handling ability and the expression of sarcomeric proteins such as myosin heavy chain (*MHC*) and troponin isoform switch (ssTnI – cTnI) (Siedner et al., 2003).

From mechanical force to haemodynamics strain

The heartbeat is generated by electrical and mechanical signals. Each contraction cycle drives not only the contraction-relaxation-shortening and elastic force of the surrounding ECM, but also the haemodynamic flow. Distinguishing between haemodynamic flow and contractile force is challenging because they are closely interconnected. However, we propose that these cues can be classified as distinct forces based on their origin, as intracardiac shear stress from the unidirectional blood flow exerts a significant impact on the lining of the cardiac walls and chambers – specially on the underlying cell populations – while contractility is primarily generated by the myocardium and propagates throughout the cardiac tissue (Goddard et al., 2017; Midgett et al., 2017). In fact, zebrafish experiments have shown that intracardiac flow dynamics regulate valve morphogenesis independently of myocardial contractility (Kalogirou et al., 2014). Furthermore, reduction in atrial volume capacity and haemodynamic changes resulting from atrial ligation in experimental surgery lead to a variety of morphological defects in embryonic chick hearts, thereby supporting the classification of these forces as distinct (Alser et al., 2021). The developing heart must adapt and adjust to the changing pressure levels required for the cardiac development (Münch & Abdelilah-Seyfried, 2021). Including the external compressive force from the epicardial sac, which contributes to cardiac volume, internal pressure and haemodynamic function (Borlaug & Reddy, 2019). Alterations in the stress-strain forces of the blood flow and pressure-volume during the early developing stages can lead to a range of detrimental effects associated with CHD (Juarez et al., 2023; Trimarchi et al., 2024).

During cardiac looping, which occurs after the formation of the linear heart tube, extensive cellular proliferation and differentiation lead to a septated heart via the endocardial cushion formation (Van den Hoff et al., 2001). The endocardial cushions are initially constituted of cardiac jelly in the heart tube, and act as primitive valves that modulate blood flow during initial contractions (Christoffels & Jensen, 2020; Gittenberger-De Groot et al., 2005). As the septum grows, it causes the opening of the initially cardiac jelly space in the heart, resulting in the expansion of the walls (Gittenberger-De Groot et al., 2005). As the heart undergoes looping to become a four-chambered organ, different cell populations are conditioned to dramatic morphological alterations due to the mechanical shear stress (Garita et al., 2011). For instance, decreased intracardial blood flow is associated with defects in the formation of trabeculae (Cairelli et al., 2022) and valves (Hove et al., 2003) in zebrafish and mouse models (Garita et al., 2011). The formation of the cardiac outflow tract is closely linked to the development and plasticity of vascular smooth muscle cells (Liu et al., 2019; Talwar et al., 2021). They are exposed to high mechanical strain through mechanosensing channels, such as Piezo and transient potential channels (Trp) (Duchemin et al., 2019), and trigger downstream pathways to adopt a differentiated phenotype and engage with the ECM (Talwar et al., 2021). The endocardial cells subjected to shear stress forces in zebrafish initiate morphogenetic programmes essential for EndoMT and valve development through the *KLF2α-WNT9B* signalling pathway and ATP-dependent receptor activation triggering *NFATC1* (Fukui et al., 2021). Other morphological changes may be observed as a result of haemodynamic shear stress, including the alignment of valve endothelial cells (VECs), which in turn trigger paracrine signalling in vascular interstitial cells (VICs) to promote ECM scaffold remodelling and maintain its integrity (Liu et al., 2007).

Under both fluid shear stress and loading pressure, mechanotransduction translates mechanical cues into biological signals that activate signalling pathways and epigenetic changes (Trinidad et al., 2022). Zebrafish studies show that membrane receptors (e.g. Trpv4/Trpp2) (Andrés-Delgado & Mercader, 2016), primary cilia in endocardial cells, and integrins in the myocardium are key mechanosensors that help coordinate this orchestrated balance of cell proliferation, differentiation, maturation,

and extracellular matrix deposition (Christoffels & Jensen, 2020; Heallen et al., 2020). In addition, Hedgehog pathway activation is closely linked to primary cilia, leading to Patched-1 (Ptch-1) and Smoothed (SMO) shuttle and subsequent regulation of the *GLI* gene family, which control cell proliferation and differentiation, survival, self-renewal, angiogenesis and EndoMT in mouse embryonic cells (Fitzsimons et al., 2022; Sabol et al., 2018). Biomechanical force modulates the activation of the transcription factor *KLF2α* by the Ca^{2+} channels Trpv4/Trpp2 (Andrés-Delgado & Mercader, 2016), which consequently triggers Smad7, Notch1 and nitric oxide (NO) system (NOS3/eNOS) pathways in ECs, influencing expression of genes with developmental cardiac function in mouse (Table 1) (Nadeau et al., 2010). Activation of transcription factor family *KLF2* leads to increased deposition of ECM proteins, supporting cushions and valve development, and regulation of important genes of development, such as *TBX5* and *GATA4* (Chiplunkar et al., 2013; Duchemin et al., 2019). Also, high levels of Piezo1, a well-known mechanosensory and mechanically activated protein, are found in the atrioventricular canal and outflow tract, and are required for cardiac valvulogenesis events in zebrafish, chick and mouse models (Haack & Abdelilah-Seyfried, 2016; Juan et al., 2023; Yu et al., 2022). The glycocalyx has recently been associated with laminar blood shear stress during cardiovascular development, and endothelin-1 (*ET-1*) shows differential gene expression during increased or decreased blood haemodynamics in chick embryos (Groenendijk et al., 2005). Additionally, alterations in the direction of blood flow have been shown to trigger a cascade of events that result in cardiac malformations in a venous clip model of chick embryos (Hogers et al., 1997).

Heart mass and myocyte enlargement are observed as a result of the enhanced haemodynamic load (Barbera et al., 2000). The increased haemodynamic overload and pressure are expected to affect the cardiac jelly, altering myocardial organization, affecting the ECM and overall tissue stiffness. Studies in zebrafish and chick embryos suggest that the increase in strain and shear stress activates transcription factors and signalling pathways, such as *KLF2* and TGFβ, modulating further changes downstream of the EndoMT (Andrés-Delgado & Mercader, 2016; Midgett et al., 2017). The myocardium wall thickness and tissue stiffness can support higher pressure and load capacity, as indicated by myocardial remodelling and overexpression of proteins to withstand the cyclic overloading (Siddiqui et al., 2022). In contrast, reducing the haemodynamic load during looping and chamber formation in mouse embryonic hearts leads to a reduction in myocardial wall thickness, a significant decrease in heart volume and reduced looping formation features, resulting in a more linear tube (Hoog et al., 2018). The signalling cascades allow an epigenetic cellular response to the environmental changes in the balance of physical stresses. Remodelling capacity is reduced after birth, when the transitional and hyperplastic phase begins to decline, and the fetal heart undergoes a developmental switch to a terminally differentiated cell stage, where only hypertrophic growth is observed (Bradshaw et al., 2009; Williams et al., 2014). The postnatal human heart has a specific tissue stiffness (∼10 kPa) to withstand stress and the physiological laminar flow from haemodynamics (Heallen et al., 2020).

Nuclear components and gene expression behaviour

Mechanotransduction pathways can occur through cell-ECM receptors, cell-cell junctions, and intracellularly through the cytoskeleton and nucleus. The nucleus contains dynamic protein complexes in its nuclear membrane and interior that also regulate the transcription of selected genes at times corresponding to different stages of embryogenesis (Christoffels & Jensen, 2020). The nuclear membrane structure consists of two separate layers, with the outer nuclear membrane (ONM) in physical contact with the cytoplasm and containing receptors and transmembrane proteins that are connected to the cytoskeleton and sarcolemma. The inner nuclear membrane (INM) faces the interior of the nucleus and links transmembrane proteins to an underlying peripheral lamina (Coscarella et al., 2023; Poleshko et al., 2017). Whereas the nuclear lamina provides support, shape and structure to the nucleus, protecting it from nuclear rupture and the loss of DNA repair factors, it also acts as an additional layer to regulate gene expression. A recent study in fibroblasts has shown that mechanical forces induced by actomyosin tension in response to the microenvironmental changes can lead to modifications in nuclear morphology, shuttling of epigenetic factors, and lamina remodelling (Alisafaei et al., 2019). The nuclear lamina has a crucial effect on chromatin organization, particularly at the nuclear periphery, which contributes to gene expression and silencing in cardiovascular cells (Lityagina & Dobreva, 2021).

But how do changes in the myocardial microenvironment influence cell behaviour and gene profiling? First, these changes are modulated by active contraction, passive stretching with the expansion of the myocardium and ECM, and mechanical pressure from blood flow during the heart formation. Mechanosensors will sense and transform these biomechanical signals into regulatory responses that act directly or indirectly in the cellular response (Gaetani et al., 2020). These regulatory responses can vary according to functional presentation; for example, the Notch pathway activation is effected by cell-cell transmembrane receptors. When physical interaction between receptors occurs, it triggers the cleavage

Table 1. Summary of the signalling pathways linked to their biomechanical origin and associated activation cascades.

Signalling Pathway	Activation	Effect	Biomechanical Origin	Reference
Hedgehog	Shear stress activates pathway by mechanical cues on primary cilium, stimulating transcription of genes	Stimulates specific regions on migratory path, proliferation, polarity, and differentiation	Haemodynamics	(Wang et al., 2010; Nadeau et al., 2010; Egorova et al., 2011; Goddard et al., 2017; Goumans & ten Dijke, 2018; MacGrogan et al., 2018; Stassen et al., 2020; Fitzsimons et al., 2022)
TGF-β	Flow stress activates TGF-β in non-ciliated cells, promoting activation of specific TFs	Drives EndoMT, differentiation, and maturation		
Notch	Blood flow induces ligand transcription and activation in neighboring cells, stimulating pathway that promotes transcription of genes	Cell fate, including ECM homeostasis, cell and tissue morphogenesis, and cell and tissue mechanics		
eNOS/NOS3	Mechanical stimuli activates expression of eNOS/NOS3, producing NO and promoting expression of genes from developmental programmes with cardiac function	Cell survival and differentiation, and atrial septum formation		
WNT	Fluid stress induces KLF2 expression, regulating flow-responsive genes, such as eNOS and WNT9B	Signals neighbouring cells that are not in direct contact with blood flow to differentiate, and mature, developing functional valves		

(*Continued*)

Table 1. (Continued)

Signalling Pathway	Activation	Effect	Biomechanical Origin	Reference
TGF-β	Intercellular strength induces secretion of TGF-β, which activates signalling cascade promoting gene transcription	Endocardial cushion formation, EndoMT, ventricular development and myocardial maturation	ECM	(Rose et al., 2010; Cheng et al., 2013; Andrés-Delgado & Mercader, 2016; Dronkers et al., 2020; Bornhorst & Abdelilah-Seyfried, 2021; Arriagada et al., 2024)
Integrin β1/ β-catenin	Fibronectin-integrin signaling stimulates activation of precardiac expression	Cardiac mesoderm emergence, cell fate and polarity		
Hippo YAP/TAZ	Cytoskeletal tension and stretch resulting in the regulation of TFs	Cardiomyocyte proliferation, heart size, myofibroblast differentiation and cell fate		
MAPK ERK/p38/JNK	Sequential phosphorylation series initiated at membrane proteins, leading to regulation of TFs and gene expression	Induction EndoMT, cell cycle activation, formation of outflow tract/trabeculation/valve, non-cardiomyocyte proliferation and hypertrophy		
Unknown	Early Ca^{2+}oscillations promote spontaneous electrical activity via NCX	Heartbeat initiation leads to early premyofibril formation and structure organization		
Unknown	Heartbeat induces cyclic stretch on premyofibrils, leading Z-bodies alignment and sarcomeric protein expression	Myofibril organization, increase of sarcomeric protein expression levels, regulation of thin and thick filament mechanics	Contractile Force	(Janowski et al., 2006; Sparrow & Schöck, 2009; Granados-Riveron & Brook, 2012; Sewell- Loftin et al., 2014; Samsa et al., 2015; Tyser & Srinivas, 2020; Ichise et al., 2022; Chen et al., 2024)
Notch	Cyclic strain activates Notch1b along with shear stress forces	Promotes ventriculobulbar valve development, and EndoMT events		

of an intracellular domain that acts as a transcription factor, regulating the expression of specific genes for morphogenesis, EndoMT, integrins, and ECM expression (Stassen et al., 2020). While integrins, focal adhesions, ion channels, receptor kinases, and phosphatases can activate differently, the regulatory responses to the cytoskeleton and other components are similar (Garoffolo & Pesce, 2019). At the cellular level, some of the signalling responses are associated with the cytoskeletal proteins – filamentous actin, microtubules or intermediate filaments – and propagate to the nucleoskeleton through nuclear membrane proteins, providing a direct connection to the interior of the nucleus and nuclear lamina (Tajik et al., 2016). An important player in bridging these connections is the LINC complex (linker of nucleoskeleton and cytoskeleton), which creates a physical connection between nucleoskeleton and cytoskeletal components and plays a key role in the transmission of force signals to withstand environmental changes (Fig. 3) (Gaetani et al., 2020; Kervella et al., 2022; Majkut et al., 2014).

The cytoskeletal proteins desmin (intermediate filaments) and microtubules stabilize the cellular structure, preventing nuclear collapse under mechanical tension and external forces. An elegant study shows that nuclear integrity is compromised with contractile force, and the disruption of intermediate filaments and microtubules drives nuclear membrane infolding, loss of genome organization, DNA damage and alterations in cardiomyocyte function (Heffler et al., 2020). Microtubules not only provide resistance to biomechanical activity, but their α-tubule detyrosination is desmin-dependent and contributes to optimal spatial compression resistance and cardiac function (Robison et al., 2016). Moreover, filamentous actin assists the nucleus positioning and regulates actomyosin contraction, playing a role in nuclear deformation and chromatin organization. Alterations in the actin cytoskeleton lead to a reduced nuclear volume and chromatin accessibility (Davidson & Cadot, 2021). Experiments in isolated nuclei demonstrated a nuclear response to tension applied directly to one of the components of the LINC complex (Nesprin-1) (Guilluy et al., 2014). These results indicate that the cytoskeleton and the LINC complex are critical for the mechanotransduction of force to the nucleus. The changes associated with the nuclear response to force can be translated into nuclear stiffening, which is also correlated with nuclear lamins and chromatin states (Lityagina & Dobreva, 2021).

The direct interactions of the nuclear lamina with transmembrane proteins provide a crucial link between the cytoskeleton and the lamina-associated domains (LADs) and chromatin territories. The nuclear lamina is a network formed by three filamentous proteins, lamin A/C (type A-lamins), B1 and B2 (type B-lamins). This

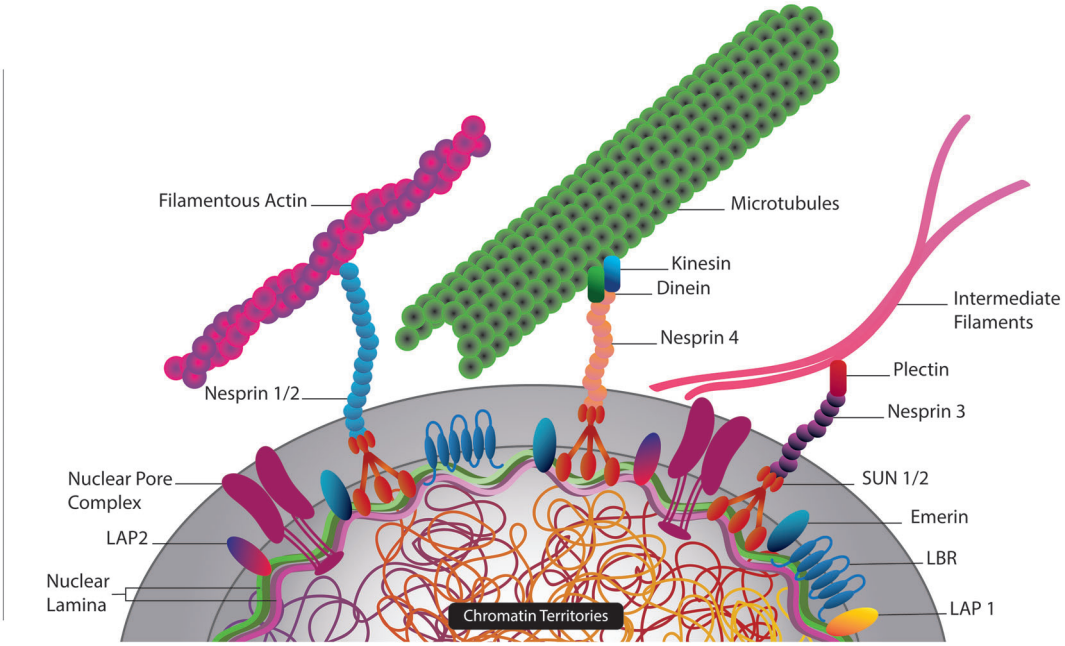

Figure 3. Nuclear membrane and the components of mechanotransduction pathways
The figure shows cytoskeletal proteins – filamentous actin, microtubules, and intermediate filaments – interacting with respective nesprin subtypes associated with the LINC complex, which connect to transmembrane SUN 1/2 proteins. These interact directly with the underlying nuclear lamina (composed of lamins A/C, B1 and B2). The lamina has anchoring sites to the chromatin that contribute to the organization of chromatin territories. Other nuclear membrane proteins that interact with the nuclear lamina are shown: LAP1, LAP2, LBR, emerin and the nuclear pore complex.

network provides a secondary spatial organization to the genome, where the LADs localize to the genome and interact to form a transcriptionally repressed region of heterochromatin (Coscarella et al., 2023; Shah et al., 2023). LADs are regulated domains located in the chromatin and nuclear lamina that are involved in regulating genes involved in cell identity and organogenesis. While non-LAD genes typically express high levels of transcription, gene expression can change from non-LAD to LAD during developmental stages; as differentiation, specification and maturation are processes that require a complex stoichiometry of gene expression (Shah et al., 2023). The ability of the nuclear lamina to regulate gene expression controls genomic access to cellular fate. Non-cardiac fate genes regions are directed to the nuclear lamina as cardiac cells gain identity, and pluripotent regions of the genome containing *Oct4*, *Sox2* and *Nanog* gain access to the lamina when stem cells differentiate (Poleshko et al., 2017). As the myocardial ECM environment, contractility rhythm and haemodynamics play major roles in regulating cardiac cell migration, differentiation, proliferation and maturation, we propose that the nuclear lamina may also be related to the mechanotransduction pathways during developmental phases (Swift et al., 2013). As a matter of fact, there is considerable evidence that the nuclear lamina modifies gene expression in the early stages of embryonic development (Constantinescu et al., 2006; Dechat et al., 2008; Kervella et al., 2022; Sullivan et al., 1999; Swift et al., 2013). We speculate that the regulation of gene expression and the remodelling of the nuclear lamina most likely work together to promote cardiac differentiation and maturation.

Differential expression of lamins has been reported in *Drosophila* and chick embryo development, showing that lamin A/C levels are particularly high at later stages and correlate with cellular differentiation and maturation phases (Dechat et al., 2008). Also, the ablation of type-A lamins (*LMNA*) in mice models results in retardation of postnatal growth and severe muscular dystrophy, a characteristic pathology that indicates that the nuclei are unable to withstand mechanical stress and become structurally compromised (Sullivan et al., 1999), along with filamentous actin disassembly (West et al., 2023). In the developing heart, the increased expression of lamin A/C is associated with the downregulation of *Oct3-4*, *Tra 1-60*, *Tra-1-81* and *SSEA-4*, which are specific markers of pluripotency, suggesting that A-type lamins may only appear after commitment of cell differentiation in animal and human models (Constantinescu et al., 2006). Whereas lamin B1 remains stable throughout maturation in both proliferative and non-proliferative states, lamin B2 levels decrease postnatally. Downregulation of lamin B2 reduces nuclear pore breakdown, nuclear translocation and regeneration, and leads to polyploid cardiomyocytes (Han et al., 2020; Vergnes et al., 2004; West et al., 2023). On the other hand, the upregulation of lamin B2 improves overall cardiac regeneration (Han et al., 2020). This intricate interplay of nuclear lamins and chromatin organization exposes the greater involvement of mechanical stress with mechanotransduction mediated pathways (from intracellular or extracellular stimuli).

Mechanotransduction effects are likely to play a pivotal role in the activation of key genes critical for myocardial development and maturation not only in cardiomyocytes, but also in non-myocyte cells within the heart. Cardiomyocytes comprise approximately 30%–40% of the total cell population in the human heart and represent 70%–80% of the cardiac mass, yet ECs and fibroblasts are also essential components of the heart (Zhou & Pu, 2016). ECs and fibroblasts are constantly subjected to mechanical stress and play a significant role in supporting cardiomyocyte function. In particular, ECs are regulators of contractile force by sensing shear stress and transmitting signals to the surrounding cardiomyocytes through paracrine factors (Hsieh et al., 2006). Additionally, ECs maintain open chromatin to promote transcription of cardiac myofibrillar genes, potentially stimulating the myocardial homeostasis (Helle et al., 2021; Yucel et al., 2020). Cardiac fibroblasts, as the primary source of ECM components and key players in cell-cell communication, are actively modulated by mechanical force through integrins and ion channels (Camelliti et al., 2005; Souders et al., 2009; Ravenscroft et al., 2016). Furthermore, fibroblast nuclei can alter gene expression in response to external mechanical stimuli (Pesce et al., 2022; Saucerman et al., 2019; van Wamel et al., 2000). Therefore, non-myocytes seem to be fundamentally important in sensing mechanical cues, maintaining cardiac microenvironment and function. There are still significant gaps in our understanding of how mechanotransduction impacts cell behaviour, and exploring this complex signalling network and its downstream effects on gene expression will enhance our understanding of cardiac health.

Therapeutic potential: regeneration *versus* maturation

Although there are many players in the maturation process of the heart, biomechanical stimuli are crucial to various developmental aspects of cardiogenesis. For example, the interaction between the contractile cytoskeleton and the nuclear lamina is important to promote the opening of nuclear pores and the successful translocation of YAP/TAZ into the nucleus (Elosegui-Artola et al., 2017; Gaetani et al., 2020). Here, we suggest that identifying the mechanical forces associated with nuclear lamina regulation at determined developmental stages will yield significant insights. By selectively controlling

which maturation regulators are activated or suppressed, we could selectively induce and/or prolong the cardiac proliferation phase.

New methodologies to achieve further levels of maturity in the pluripotent stem cell-derived cardiomyocytes (PSC-CMs) model have been developed in recent years (Ahmed et al., 2020). Although these methods have helped improve maturation to some degree, the overall cellular profile of PSC-CMs is still locked in a perinatal phenotype, suggesting a maturation arrest (Kannan et al., 2023). Thus, a comprehensive analysis is needed to identify additional molecular pathways that are intrinsically involved in the development and maturation processes of cardiomyocytes. Given the crucial role of mechanical forces in cardiac morphogenesis, exploring the effects of lack of mechanical stimuli under *in vitro* conditions may provide further answers. Cultivation of cardiomyocytes that are exposed to mechanical strain and more closely resemble physiological conditions may enhance current cardiac differentiation methods, resulting in a cell product with a higher rate of success in clinical therapies. Currently, clinical limitations in this application include immature cardiomyocytes that can cause arrhythmias, immunogenicity, and poor engraftment in patients with heart failure (Selvakumar et al., 2022). A better understanding of mechanotransduction effects in cardiomyocyte development is needed to enable novel therapeutic approaches in cardiovascular diseases and the improvement of PSC-CMs therapies.

Conclusions

Mechanical forces are intrinsic and essential for the heart development. The events of cardiogenesis are influenced by many factors, and mechanotransduction can translate force input into biochemical responses by triggering signalling pathways, interacting with the nuclear lamina, and ultimately inducing genetic changes. Many studies have demonstrated that cells employ this dynamic process to sense and respond to their local microenvironment by expressing specific genes and promoting differentiation and maturation at specific time points. These dynamic biomechanical changes are most prominent during embryogenesis, when cellular layers are highly proliferative, and blood flow, ECM mass and contractile machinery begin to develop, until full maturation of the heart. Also of key importance are the associated roles of chromatin reorganization and the nuclear lamina in engaging the transcriptional regulation necessary for heart formation.

The complexity of interactions that are part of the mechanotransduction pathway and gene activation are relatively unknown. However, new technologies pave the way for innovative methodologies, such as diffusion gradients, micromanipulation, and hydrogels, to investigate cues that govern cardiogenesis (Mandrycky et al., 2020). We believe that exploring the effects of lamina interactions on chromatin regulation has great potential for significant advancements in the regenerative medicine approaches used in future cardiovascular research and clinical applications. Since cardiac regeneration is only observed during the fetal-neonatal stage, understanding the factors in the physiological microenvironment that selectively induce maturation could potentially provide us with the right tools to prolong the proliferative phase, thereby allowing repair and regeneration in the heart. At the same time, it would allow researchers to apply mechanical force techniques to the culture of PSC-CMs, with the aim of producing high quality, more physiologically functional mature cells. Ultimately, applying these insights could revolutionize our current approaches towards cardiac repair and regeneration, bringing new possibilities of treatment that could ameliorate the recovery and outcomes for patients with cardiovascular diseases.

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Additional information

Competing interests

The authors declare no conflict of interests.

Author contributions

Both authors discussed and contributed to the final manuscript. I.L.C. designed and wrote the manuscript; C.K. contributed with writing and supervised the final version of the manuscript. Both authors agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

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