Published in final edited form as:

Nat Rev Cardiol. 2019 June ; 16(6): 361–378. doi:10.1038/s41569-019-0155-8.

Mechanical regulation of gene expression in cardiac myocytes and fibroblasts

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Abstract

The intact heart undergoes complex and multiscale remodelling processes in response to altered mechanical cues. Remodelling of the myocardium is regulated by a combination of myocyte and non-myocyte responses to mechanosensitive pathways, which can alter gene expression and therefore function in these cells. Cellular mechanotransduction and its downstream effects on gene expression are initially compensatory mechanisms during adaptations to the altered mechanical environment, but under prolonged and abnormal loading conditions, they can become maladaptive, leading to impaired function and cardiac pathologies. In this Review, we summarize mechanoregulated pathways in cardiac myocytes and fibroblasts that lead to altered gene expression and cell remodelling under physiological and pathophysiological conditions. Developments in systems modelling of the networks that regulate gene expression in response to mechanical stimuli should improve integrative understanding of their roles in vivo and help to discover new combinations of drugs and device therapies targeting mechanosignalling in heart disease.

Physiological and pathological cardiac structural remodelling are commonly associated with chronic alterations in haemodynamics, chamber shape and myocardial mechanics that can initially compensate for, but ultimately exacerbate, the physical triggers of cardiac remodelling[1,2]. Cell-mediated mechanotrans-duction responses are important regulators of adaptive and maladaptive myocyte and matrix remodelling[3]. Mechanical loading also induces the release of factors such as angiotensin II, endothelin 1 and transforming growth

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Author contributions

All the authors researched data for the article, discussed its contents and reviewed and edited the manuscript before submission. J.J.S., A.D.M. and J.H.O. wrote the manuscript.

Competing interests

J.J.S., P.M.T. and K.S.B. declare no competing interests.

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Reviewer information

Nature Reviews Cardiology thanks P. Kohl and the other anonymous reviewer(s), for their contribution to the peer review of this work.

factor-β (TGFβ), which are potent activators of myocyte hypertrophy and matrix remodelling[4–6].

At the organ and tissue scales, concentric hypertrophy during pressure overload and exercise-induced physiological hypertrophy can be homeostatic or compensatory by normalizing wall stress or increasing cardiac output. These hypertrophic responses can also be accompanied by adaptive remodelling of the extracellular matrix (ECM) and coronary vasculature. In vitro studies suggest that these responses can be derived from fundamental regulatory mechanisms that drive normal sarcomerogenesis and match ventricular structure to mechanical workload demands[7]. However, under pathological conditions, myocardial mechanoregulated remodelling responses frequently become maladaptive, leading to decompensation and failure associated with elevated wall stresses, insufficient or inappropriate cardiomyocyte hypertrophy, apoptosis, pathological fibrosis or energetic mismatches between supply and demand[8–10]. Haemodynamic loading itself is an important therapeutic target, and mechanical unloading with left ventricular assist devices (LVADs) or other device strategies can, under some conditions, reverse changes in gene expression and structural remodelling and partially restore ventricular function[11–13].

Cardiac tissue remodelling is regulated by multiple cell types, including cardiomyocytes, fibroblasts, endothelial cells, smooth muscle cells and haematopoietic-derived cells. Endothelial cells constitute the majority of non-cardiomyocytes in the heart[14] and are involved in multiple regulatory and disease responses in the myocardium. Because of the central roles of cardio-myocytes and fibroblasts in cardiac structural remodelling, in this Review, we focus on these cell types and their responses to multiple biomechanical signals[15–17], although other cells types are clearly also mechanoregu-lated. The cellular mechanosensors, signalling pathways, timescales and functional responses share similarities between these two cell types. Fibroblast–cardiomyocyte crosstalk during mechanical stimulation is clearly present and important, although still not fully understood[18,19]. All whole-tissue and many in vitro studies reflect the combined gene-expression response in myocytes and non-myocytes.

Cardiac myocytes and fibroblasts have been shown to respond to a variety of mechanical stimuli, including static and dynamic, isotropic and anisotropic, compressive and tensile stresses and strains, as well as fluid flow shear stresses and alterations in substrate stiffness. The features of the mechanical stimulus can induce distinct signalling mechanisms and gene-expression profiles. A variety of molecular mediators and pathways have been identified. Regardless of the specific experimental system or stimulus, there seem to be common mechano-regulated gene programmes, such as the re-expression of fetal gene programmes[20] and the induction of genes encoding ECM[21] and cytoskeletal proteins[22], suggesting that these genes might be critical in the remodelling responses of the heart to altered mechanical conditions. We review the major pathways shown to be mechano-regulated and the major downstream transcriptional responses in cardiac myocytes and fibroblasts (FIG. 1).

Nevertheless, how these numerous mechanical signals and pathways are integrated in vivo, and how they determine hypertrophic versus fibrotic responses, eccentric versus concentric

hypertrophy, hypertrophic versus dilated cardiomyopathy[23,24], compensated versus decompensated adaptation, or heart failure with reduced ejection fraction versus heart failure with preserved ejection fraction remains poorly understood[25,26]. Therefore, we also emphasize the need for more integrative analyses of mechanoregulatory mechanisms in cardiac cells and discuss new, integrative approaches to analysing cardiac cell mechanosignalling that promise to advance this synthesis. Given that these approaches need to account for the wide variety of mechanical stimuli, mechanosensors, signalling pathways, and transcriptional and phenotypic responses, we conclude by surveying new systems biology approaches, such as multiscale computational models that promise to advance our understanding of the relationships between altered cardiac wall mechanics, changes in gene expression, and chronic tissue and chamber remodelling.

Cardiac mechanosensitive pathways

The myocardium in adult mammals is a structurally complex tissue composed of many cell types, including myocytes, fibroblasts, endothelial cells and perivascular smooth muscle cells. Myocytes make up >70% of the myocardial volume, but only 25–40% of the cells by number[14,27]. In this section, we review cardiac cell structural and functional pathways that mediate mechanosensitive responses in two predominant and well-characterized cell types in the heart: myocytes and fibroblasts. These pathways are especially active during cardiac growth and development and are downregulated under normal homeostatic conditions in adults. Many pathways are also altered or reactivated by abnormal or pathological conditions in the mature heart. Mechanosensing and the subsequent signalling processes and gene expression are associated with structures and protein complexes on the surface of, inside and between these cells (FIG. 1).

Cell membrane and downstream pathways

The integrin complex in cardiac myocytes.—Transmission of forces between the interior and exterior of cardiac myocytes is facilitated by transmembrane proteins such as integrins and their associated intercellular complexes. Forces generated by the contractile filaments are transmitted outside the cell through this complex and, likewise, cells sense external mechanical cues via these connections. Integrins are receptors that form dimers with α and β subunits, which can bind to ECM proteins, including fibronectin, laminin and collagen[28]. In response to pressure-overload-induced hypertrophy, the expression of α1, α5, α7 and β1D integrin subunits increases[29]. Hearts deficient in β1 integrin have a blunted hypertrophic response to transverse aortic constriction (TAC)[30]. Integrins are connected to intracellular signalling proteins, such as integrin-linked protein kinase (ILK), an important regulator of sarcoplasmic/ endoplasmic reticulum calcium ATPase (SERCA) and phospholamban, which both regulate cardiomyocyte contractility[31].

The costamere is an organized membrane complex localized at the Z-disc in muscle cells that incorporates integrins and other proteins such as vinculin and talin, mechanically linking cytoskeletal structures and the sarcomeres to the sarcolemma and ECM[32]. Forces at the costamere not only cause cell deformations[33] but also induce activation of vinculin, focal adhesion kinase (FAK), proto-oncogene tyrosine-protein kinase SRC and the small GTPase

RhoA[34,35]. Vinculin also localizes to the intercalated disc, which has made it harder to isolate the specific function of vinculin in mechanotransduction[36]. Vinculin heterozygous-null mice have decreased cardiac function after 6 weeks of TAC[37]. Mice deficient in talin 1 have a blunted hypertrophic response to TAC[38]. Talin can recruit FAK to the costamere[39]. FAK is an important regulator of cytoskeletal organization and hypertrophic gene expression[40], has been shown to mediate integrin signalling leading to hypertrophy and is activated by α_1-adrenergic stimulation[41]. In addition to its function at the costameres, FAK and its carboxy-terminal-binding partners p130 CRK-associated substrate (p130Cas) and paxillin also translocate to the Z-disc with hypertrophy. Therefore, the assembly of signalling complexes that include the costameric proteins as well as p130Cas, FAK and paxillin at Z-discs might regulate, either directly or indirectly, both cytoskeletal organization and gene expression associated with the cardiac myocyte hypertrophic stretch response[40].

The integrin complex in fibroblasts.—Cardiac fibrosis and the accumulation of ECM is found in almost all forms of cardiac disease[42], and the transformation of cardiac fibroblasts to myofibroblasts and their regulation of tissue fibrosis and ECM is mediated by a variety of chemical and physical stimuli[43]. The ECM is an important mediator in the regulation of cell surface growth factor receptors and adhesion molecules in fibroblasts, such as integrins[43]. When cardiac fibroblasts bind to ECM ligands, these cells can sense and respond to mechanical signals via membrane receptors, including integrins, which cluster to form focal adhesions. In fibroblasts, the focal adhesion–integrin complex is a primary mechano-sensing organelle[44]. Integrins interact with >150 known partners, making the focal adhesion complex the initiator of many downstream signalling pathways[45]. These pathways include crosstalk with other membrane receptors, including G-protein-coupled receptors and tyrosine kinase receptors[46,47].

Activation of fibrotic signalling depends on specific integrins[48] and ECM ligands[43,49]. Multiple components of the focal adhesion complex and their interactions result in fibrosis-related signalling cascades in response to mechanical stimuli. Integrins also directly activate non-receptor tyrosine-protein kinases, such as FAK, SRC and FYN in response to mechanical cues[49,50], and pathways such as mitogen-activated protein kinases (MAPKs) and p38 (REF.[51]), leading to ECM production and fibrosis[52,53]. Therefore, strong feedback exists between integrin-mediated responses to the stretched ECM and the fibroblast-mediated remodelling of ECM synthesis, degradation and crosslinking[49], as discussed further below.

The dystroglycan complex in cardiac myocytes.—The dystroglycan complex is another mechanical link between the cardiomyocyte cytoskeleton and the ECM[54]. Proteins associated with this transmembrane complex include dystrophin, sarcoglycans, dystroglycan, dystrobrevins, syntrophins, sarcospan, caveolin 3 and neuronal nitric oxide synthase[54]. Dystroglycan attaches to the actin cytoskeleton via dystrophin[55] and connects externally to the ECM protein laminin[56]. Dystrophin mutations lead to Duchene muscular dystrophy[57,58], and force production and power output are substantially reduced in the skeletal muscle of dystrophin-deficient mice[59]. Disruption of the dystrophin–dystroglycan

complex impairs the capacity of cardiomyocytes to produce nitric oxide and might increase cell slippage and chamber dilatation in response to stretch[60,61].

Changes in gene expression in models with dystro-glycan complex defects are consistent with an inflammatory response[62] and involve genes encoding both cellular (actins, cardiac ankyrin repeat protein (CARP; also known as ANKRD1) and cathepsins) and ECM (procollagens, biglycan, matrix metalloproteinases and tenascin C) proteins[54]. Genes in metabolic and energetic pathways tend to be downregulated[63].

Mechanosensitive channels in cardiac myocytes.—Many mechanoregulated responses, such as mechanoelectric feedback, in cardiac myocytes have been attributed to stretch-activated ion currents. Mechanosensitive channels are important mediators of sarcolemmal stretch sensing and have been implicated in arrhythmias induced by acute and chronic changes in cardiac mechanical loading[64]. Mechanosensitive ion channels have been reported in the sarcolemma and transverse-tubule system in cardiac myocytes and regulate transmembrane fluxes of sodium, potassium, calcium and chloride ions[64].

Intracellular calcium release was reported in some of the earliest studies of myocyte responses to acute stretch[65–67], but it has taken many years to identify the origins of this calcium. Among the calcium channels claimed to be stretch-sensitive, the L-type calcium channel (LTCC)[68–70] and members of the transient receptor potential (TRP) channel family[71–73] have the most evidence. As is the case with angiotensin II receptor activation, calcium release triggers the upregulation of a wide range of hypertrophic factors[74]. Many of these calcium-dependent effects are mediated by the calcineurin–nuclear factor of activated T cells (NFAT) pathway[75,76]. Importantly, the mechanosensing capacity of cardiac calcium and other ion channels has relevance for electrophysiology as well as cellular hypertrophy[77]. As further studies clarify the role of LTCCs and TRP channels in the heart, their pharmacological relevance will continue to increase[78].

Mechanosensitive channels in fibroblasts.—Although well documented in cardiac myocytes, mechanosensitive channels in cardiac fibroblasts and their role in regulating cell function are not as clear. Cardiac fibroblasts express several ion channels that are not necessarily mechanically sensitive (Nav1.5, KATP and BKCa)[79], but fibroblasts might have stretch-activated ion currents through channels such as TRPs[64] and other nonselective cation conductance channels[80] that might affect mechanoelectric feedback[81]. Other functions in cardiac fibroblasts, such as myofi-broblast differentiation in response to TGFβ and matrix stiffness, are regulated by mechanosensitive ion channels, such as TRPs generally[82] and TRPV4 specifically[83], and involve downstream signalling of AKT, SMAD and myocardin-related transcription factor A (MRTF-A) pathways. Studies in mouse pressure-overloaded hearts have shown that inhibition of TRPC3 activity reduces fibrosis, suggesting a role for these types of stretch-sensitive ion channels in fibrosis signalling[82]. Studies have also suggested that mechanosensitive TRPV4 channels are involved in the integration of mechanical and TGFβ signals into myofibroblast differentiation[84] and thereby the cardiac fibrosis response.

Calcium-related signalling in cardiac myocytes.—In addition to its well-described function in excitation–contraction coupling, calcium is an important second messenger in the regulation of metabolism, apoptosis and transcription[85]. A variety of external and internal mechanical loads affect intracellular calcium signalling[86]. Stretch induces transient increases in intracellular calcium[87,88] and sarcoplasmic reticulum calcium spark rate[89] via multiple mechanisms, including the influx of calcium via membrane channels (as described above), triggering sarcoplasmic reticulum calcium release via ryano-dine receptors[87]. Studies suggest that stretch induces an increase in reactive oxygen species (ROS) in a process dependent on membrane-bound NADPH oxidase 2 (NOX2) and microtubules (termed X-ROS signalling), which increases the calcium sensitivity of ryanodine receptors and the frequency of calcium sparks[90]. This stretch-induced X-ROS signalling has been associated with arrhythmia and diseases such as muscular dystrophy[91]. Myofilaments can also supply the increase in intracellular calcium via load-dependent changes in myofilament calcium sensitivity[92] or by crossbridge detachment leading to calcium dissociation from troponin C[93]. Elevated intracellular calcium can increase protein kinase C (PKC), calcineurin and calcium–calmodulin-dependent protein kinase II (CaMKII) signalling and thereby lead to downstream gene-expression changes[85]. Calcium dynamics in atrial myocytes are also sensitive to mechanical stimuli, possibly mediated by a surface-membrane-associated compartment[94].

Several calcium-related pathways are associated with regulation of cellular hypertrophy and might be one mechanism by which cardiac myocytes sense external loads and respond with long-term gene regulation and cell growth. The calcium–calmodulin pathway regulates hypertrophic signalling and myocyte growth[95]. Related to calcium signalling and cardiac hypertrophy are the CaMKII–histone deacetylase (HDAC) and calcineurin–NFAT pathways. HDACs can be regulated by hypertrophic stress signals[96] and have been associated with transcription factors including activator protein 1 (AP-1), activating transcription factor 1 (ATF1), serum response factor (SRF), cAMP-response element binding protein (CREB) and myocyte enhancer factor 2 (MEF2)[97]. NFAT signalling is downstream of calcineurin and low-frequency calcium changes[98]. Several hypertrophic pathways are related to NFAT signals via transcription factors such as GATA4 (REF.[99]), and calcium-dependent calcineurin–NFAT pathway activation by stretch in myocytes is implicated in cellular hypertrophy[100].

Calcium-related signalling in fibroblasts.—Stretch-activated ion channels in cardiac fibroblasts create an early signal within the cell that is responsive to stretch of the membrane[101]. Deformation of the fibroblast membrane is associated with fluxes of calcium and other ions, and the calcium influx is seen in various cell-stretch studies and is associated with fibrosis in the tissue[21]. Increases in calcium signals activate multiple signalling pathways in fibroblasts including MAPK signalling[102] and CaMKII pathways, which activate transcription factors, such as CREB[103]. The TRPC6 calcium channel in fibroblasts has been shown to be critical for myofibro-blast differentiation via angiotensin-II-stimulated and TGFβ-stimulated calcineurin pathways[104].

Angiotensin II signalling in cardiac myocytes.—Angiotensin II has multiple effects in the myocardium, and specific signalling pathways have been discovered in cardiac myocytes. Angiotensin II, via specific angiotensin II membrane receptors, mediates cardiac contractility, coupling between myocytes and electrical propagation, and long-term regulation of growth and remodelling[105]. Angiotensin II is likely to be produced and released by cardiac myocytes, in particular under pathological conditions[106]. The angiotensin II type 1 receptors (AT1Rs) start the signalling cascades associated with angiotensin II in the heart and are associated with short-term blood-pressure control and long-term cardio-myocyte growth. AT1R was one of the first molecules implicated in cardiac mechanosignalling[107,108]. In cardiac myocytes, angiotensin II directly leads to cell growth, but this effect is mostly seen in neonatal cells rather than in adult myocytes[109]. In response to stretch, AT1R signalling increases MAPK phosphorylation[110,111], JAK–STAT signalling[112,113] and expression of several hypertrophic markers[107,114]. Studies have also shown that matrix metallo-proteinase (MMP) expression by cardiac myocytes is angiotensin-II-dependent[115]. AT1R has also proved to be directly stretch-sensitive, independent of the binding of ligands such as angiotensin II[116]. AT1R signalling via G-protein-coupled pathways is biased to β-arrestin-mediated pathways during mechanoactivation, suggesting that myocyte stretch can mediate AT1R signalling with or without ligand binding[14,117–119]. Interestingly, β-arrestin activity in coordination with AT1R was shown to mediate the Frank–Starling mechanism of cardiac contractility[120]. Although cardiomyocytes do release angiotensin II in response to stretch[107,108,110,121,122], both the mechanism underlying angiotensin II release and its specific effect on cardiomyocyte remodelling remain unclear[123]. Nonetheless, the importance of angiotensin II and AT1R in cardiomyocyte mechanosensing is firmly established, especially given the prevalence and efficacy of AT1R blockers for treating cardiovascular disease[124].

Angiotensin II signalling in fibroblasts.—Angiotensin II has well-documented profibrotic effects in cardiac fibroblasts[125]. Angiotensin II can regulate cardiac ECM via an increase in collagen expression through activation of AT1Rs[126,127]. This type of fibrotic response is likely to be mediated through TGFβ synthesis and related path-ways[128,129]. Evidence exists for both direct downstream activation of TGFβ by angiotensin II and via paracrine mechanisms[130,131]. Angiotensin II also exerts its profibrotic effects by decreasing MMP activity[132] and increasing tissue inhibitor of metalloproteinases (TIMP) activity[133]. Pathways that have been associated with angiotensin II signalling in the heart include syndecan[17], IL-6 and ERK– p38 MAPK–JNK[134]. Stretch and angiotensin II can mediate cytokine release from fibroblasts[135] that might further regulate fibrosis. In addition to the profibrotic effects of angiotensin II on cardiac fibroblasts, effects have also been documented on myofibroblast differentiation[136] and possibly proliferation of adult fibroblasts, probably via autocrine or paracrine mechanisms[137]; these path-ways involved growth factors such as vascular endothelial growth factor[138] and endothelin 1 (REF.[139]).

TGFβ signalling in cardiac myocytes.—TGFβ is well described as a contributor to fibrosis in many different tissues, including the myocardium[109], although TGFβ signalling in cardiac myocytes is not as well defined as in fibroblasts. The expression of TGFβ in cardiomyo-cytes increases in both dilated and hypertrophic cardio-myopathies[140,141]. In

cultured cardiomyocytes, TGFβ mRNA and protein are upregulated by angiotensin II[142], and TGFβ itself promotes expression of the fetal gene programme associated with cell hypertrophy[143,144]. TGFβ expression in cardiomyocytes is regulated by several molecular signals including PKC, p38 MAPK and the AP-1 complex[142]. TGFβ signalling in myocytes might also be involved in maladaptive hypertrophy and cardiac dysfunction[145]. Stretch might directly regulate TGFβ–SMAD signalling in neonatal cardiomyocytes, modulating gene expression and inhibiting cardiomyocyte proliferation during development[146].

TGFβ signalling in fibroblasts.—In cardiac fibroblasts, TGFβ is centrally involved in many aspects of fibrosis, including myofibroblast differentiation, inflammation, gene expression and ECM synthesis[147–149]. TGFβ receptors signal via SMAD proteins, which translocate to the nucleus and regulate gene transcription[150]. SMADs inter-act with a large number of DNA-binding transcription factors and therefore trigger a diverse set of gene transcription responses[151]. TGFβ also initiates transcription through noncanonical pathways including p38 MAPK, ERK, JNK, TAK1 and RhoA GTPase[147].

In addition to the many molecular signals that activate fibroblasts during injury response[152], mechanical stress stimulates TGFβ signalling in cardiac fibroblasts via regulation of ECM organization and TGFβ bio-availability. Stretched fibroblasts increase expression of TGFβ mRNA and protein[153]. TGFβ is secreted in latent form and then activated through contraction-mediated conformational changes in the integrin-latent TGFβ– ECM[154] complex[155] and by numerous other mechanisms including MMP2 and/or MMP9 proteolytic cleavage[156]. This system can involve complex feedbacks, because mechanical stretch of cardiac fibroblasts can modulate gene expression of *MMP2* and *TIMP2* (REF.[157]) as well as MMP activity[158], probably through the PKC and tyrosine kinase pathways[157]. Furthermore, mechanical loading of some ECM components, such as collagen, causes conformational changes that can shield them from MMP-mediated proteolysis[159,160]. Crosslinking enzymes, such as lysyl oxidase-like 2 (LOXL2), are upregulated in the heart in response to mechanical stress and are associated with cardiac fibrosis and increased stiffness[161]. In addition to increasing collagen organization and therefore TGFβ bioavailability, LOXL2 was found to stimulate cardiac fibroblasts to produce TGFβ, mediating TGFβ signalling. Inhibition of LOXL2 reduced cardiac fibrosis in response to left ventricular pressure overload and improved overall cardiac function[161].

Cytoskeletal complexes

The cytoskeleton has a complex structural arrangement in most cell types, and specific components have been associated with transduction of mechanical signals in cardiac myocytes and fibroblasts. Most cytoskeletal mechano-transduction processes in myocytes are associated with the sarcomere and Z-disc, whereas in fibroblasts, the actin cytoskeleton is central to these pathways (FIG. 1).

MLP, titin and associated complexes in cardiac myocytes.—Myofilament perturbations can affect mechanotransduction by altering either sarcomere contraction or calcium buffering[162,163]. The Z-disc of the sarcomere is directly connected to the cytoskeleton, but in addition to mediating force transmission[164], Z-disc-associated proteins

are now well recognized to have important functions in mechanosensing and mechanotransduction.

Titin is a giant protein that connects the Z-disc to the M-line and is responsible for the passive stiffness of cardiac muscle[165]. Titin has been proposed to be an important mechanosensor and interacts with many proteins that have been implicated in mechanosensitive signalling pathways[166]. These cytoskeletal proteins that can bind to titin include muscle LIM protein (MLP), telethonin (also known as titin cap protein; TCAP), four-and-a-half LIM domains protein 1 (FHL1) and muscle ankyrin-repeat protein (MARP) family members[167].

MLP has been widely investigated as a prime mech-anosensing element in the Z-disc, with direct binding to α-actinin[168,169]. In MLP-deficient mice, a lack of upregu-lation of fetal gene markers, such as *Nppa* (encoding atrial natriuretic peptide) and *Nppb* (encoding B-type natriuretic peptide), in response to mechanical stress suggests that MLP has a specific role in mechanotrans-duction and cardiomyocyte hypertrophy[170]. Mice deficient in MLP eventually develop heart failure and die prematurely168, possibly owing to abnormal mechano-transduction at the Z-disc. The loss of MLP and its inter-actions with TCAP have also been suggested to alter the elastic properties of titin, leading to the inability of cardiac muscle cells to sense mechanical stress properly[170]. As shown in smooth muscle cells, MLP mediates gene expression via binding to GATA and SRF transcription factors[171] and possibly modulates gene expression through similar pathways in cardiac myocytes. Additionally, MLP has also been implicated in anchoring calcineurin at the Z-disc[169], which might be part of the calcineurin–NFAT hypertrophic pathway. PKC-interacting cousin of thioredoxin (PICOT; also known as glutaredoxin 3) is a protein found at the Z-disc and has also been implicated in hypertrophic signalling via the calcineurin–NFAT pathway75. PICOT interacts with MLP, which in turn mediates the binding of calcineurin to MLP, leading to its displacement from the Z-disc.

The Z-disc giant protein titin has been shown to be an important contributor to passive stiffness of the myocardium[172]. FHL1 binds to titin at its elastic region[173] and is upregulated in animal models of hypertrophy[174,175], implicating FHL1 in the biomechanical stress responses in cardiac hypertrophy. This stress response is likely to be related to the signalosome that encompasses components of the MAPK signalling pathway RAF1–MEK2– ERK2 at the stretch sensor domain of titin[173]. Further studies have suggested a direct link between FHL1-mediated mechanotransduction and Gq pathways, with FHL1 deficiency preventing ERK2 phosphorylation caused by constitutively active G_q overexpression in a mouse model[173]. FHL1 might also act as a scaffold for MAPK-mediated hypertrophic signalling[176].

Similar to FHL1, all three MARP members, including CARP, ankyrin repeat domain-containing protein 2 (ANKRD2) and diabetes-related ankyrin repeat protein (DARP; also known as ANKRD23), bind to titin. However, MARP members bind to the N2A region instead of the N2B region. In response to stretch of neonatal rat cardiac myocytes, CARP and DARP translocate to the nucleus[177]. Additionally, eccentric contractions of skeletal

muscle cause upregulation of *CARP* and *ANKRD2* gene expression[178]. MARP members have been linked to protein kinase A and PKC[179].

Actin and associated complexes in fibroblasts.—As in other cell types, the cytoskeleton in cardiac fibroblasts is a structural network responsible for maintaining cell shape and stability and is the mechanical structure that can transmit mechanosignals both outside-in and inside-out. The ECM is a regulator of cytoskeletal stress[180], and fibroblasts have been shown to use mech-anotransduction signalling pathways from surface molecules (such as integrins) to control and maintain their actin cytoskeleton. RhoA, a member of the family of small Rho GTPases[181], activates Rho kinase (ROCK), which phosphorylates downstream targets associated with actin stress fibre regulation, including LIM kinases and myosin light chain[17]. RhoA-dependent signalling affects nuclear translocation of transcription factors in part through these changes in the actin cytoskeleton[17].

An important example of cytoskeleton-mediated control of transcription is via MRTF-A and MRTF-B. When fibroblasts undergo changes in their external mechanical environment, Gactin assembles into Factin polymers, liberating MRTF-A and allowing it to enter the nucleus[182]. Deficiency of MRTF-A reduces fibrosis after myocardial infarction[183], implicating MRTF-A as an important component of the fibrosis pathway in response to mechanical signals. Another pathway associated with cytoskeletal dynamics and sensing of ECM mechanical signals is the Hippo signalling pathway[184,185]. Inhibition of Rho and disruption of Factin results in pathway inactivation[186] and can lead to alterations in translocation of the transcription co-activators yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) between the cytoplasm and the nucleus[187]. These transcriptional co-activators, possibly interacting with SMAD3 from the TGFβ signalling pathway, might regulate fibroblast myofibroblast differentiation[188].

Nuclear mechanosensing

Cardiac myocytes.—Evidence suggests that myocyte stretch can have direct effects on the nucleus via force transmission through the sarcolemma and cytoskeleton and that mechanosensing might occur inside the nucleus of myocytes via modulation of protein activity in the nucleus[189]. The nucleus has been shown to be mechanically connected to the cytoskeleton inside the cytoplasm by linker of nucleoskeleton and cytoskeleton (LINC) complexes [190], probably mediated by nuclear lamins[191,192]. Lamins are specialized structural proteins that provide structural stability to the nucleus. Other integral nuclear membrane proteins include emerin, inner nuclear membrane protein Man1, LEM domain-containing protein 2, spindle-associated membrane protein 1, barrier-to-autointegration factor and certain transcription factors[193,194]. The LINC complex has been shown to be a direct nuclear mechanotransducer[195] and can regulate transcription factors and chromatin structure in the nucleus and, therefore, gene transcription[189]. Mutations in the proteins of the nuclear envelope can disrupt this type of force transmission and directly influence mech-anotransduction and transcriptional regulation[196]. Without the intact cytoskeleton, in particular actin filament connections to the nuclear membrane, deformation of the nucleus can occur with defective mechanotrans-duction[197]. Force distributions within nuclear lamina are altered with varying nuclear properties[192]. Laminopathies, caused by mutations in the

LMNA gene, are associated with muscular dystrophies, lipodystrophies and premature ageing syndromes[198], with an inflammatory component linked to some of these diseases[199]. Evidence also exists that stresses transmitted to the nucleus can affect chromatin structure, possibly regulating transcription factors directly[200]. In mice overexpressing high mobility group nucleosome-binding domain-containing protein 5 (HMGN5)[201], the mutation of the protein alters the interaction between H1 histone and chromatin, reducing chromatin compaction[202], which suggests a link between forces transmitted through the nuclear membrane and chromatin structure.

Fibroblasts.—Direct cytoskeletal force transmission to the nucleus might also mediate mechanically regulated gene expression in fibroblasts[190]. This mechanism is likely to be a ubiquitous and efficient way for cells to respond rapidly to external mechanical forces[17]. Studies in fibroblasts with defective lamins have shown alterations in proliferation, suggesting this nuclear structural protein has a role in fibroblast activation and probably differentiation into myofibroblasts[203]. The lamins and emerin can regulate actin function in mouse embryonic fibroblasts, regulating MRTF-A and SRF activity[204] and cardiac myofibro-blast differentiation[183]. Mechanosensing in the nucleus is suggested by changes in nuclear shape, and these shape changes have been associated with alterations in gene expression. For example, fibroblast collagen synthesis has been reported to depend on the shape of the nucleus[205]. The LINC complex is involved in nuclear mechanosensing and gene transcriptional changes in response to the altered mechanical environment of the cell[206]. Nuclear shape is associated with fibroblast cell spreading and migration speed, and this mechanosensing is defective when the LINC complex is disrupted[207].

As the heart develops and matures, the nuclei of cardiac fibroblasts and myocytes are exposed to varying degrees of mechanical forces. Therefore, in cells with a defective or fragile nuclear membrane and associated interconnections to the cytoskeleton, the nucleus can show decompacted chromatin and nuclear blebbing, as seen in cell death. These observations indicate the mechanosensitivity of nuclei and that its structural integrity is important for cardiac cell adaptation to physical loads[17].

Cell–cell interactions

Intercalated discs in cardiac myocytes.—The intercalated disc is the cell–cell junction that longitudinally connects neighbouring cardiac myocytes. The intercalated disc has multiple functions related to maintenance of mechanical and electrical coupling between cardiomyo-cytes[208,209]. In response to cyclic cardiac volume overload, the intercalated disc undergoes ultrastructural changes that might be associated with sarcomere restructuring, implicating the cell–cell junction as part of the mechano-transduction pathway associated with myocyte hyper-trophic growth[210]. The three types of cell junctions that make up an intercalated disc are fascia adherens, desmo-somes and gap junctions. Fascia adherens are anchoring sites for cytoskeletal actin and connect to the closest sar-comere. Intermediate filaments bind to desmosomes[209]. Ions can pass through gap junctions, which allows action potentials to propagate along muscle fibres.

The fascia adherens junctional complex is composed of proteins such as cadherins, catenins and catenin-binding proteins[211]. N-Cadherin (also known as cadherin 2) can form attachment sites with neighbouring cardiac myocytes and transmit forces between cells[212]. N-Cadherin has also been shown to be upregulated in response to stretch[213]. Hearts from N-cadherin-deficient mice have altered cell–cell mechanosensing that affects their sarcomere structure and causes dilated cardiomyo-pathy[214]. Cardiac myocytes from these mice do not have identifiable fascia adherens junctions, and their sarcomeres are shorter in length. β1 Integrin levels are increased in hearts from N-cadherin-knockout mice, which indicates a compensatory response in which other mechanotransductive proteins increase in expression owing to the deficit of N-cadherin[214]. Catenins are also part of the fascia adherens junctional complex and regulate cadherin-based and binding proteins, such as muscle-specific mouse mXinα, vinculin–metavinculin and α-actinin, which link the fascia adherens to the cytoskeleton and modulate catenin activity[211,212]. α-Catenin recruits vinculin to the fascia adherens junction through force-dependent changes in α-catenin[215]. α-Catenins have also been shown to modulate cytoskele-tal mechanotransmission, which can regulate YAP-mediated cell proliferation during development[216]. As with deficiency of N-cadherin, α-catenin deficiency alters the structure of the intercalated disc and leads to dilated cardiomyopathy. Vinculin localization is lost at the fascia adherens junction; however, vinculin also localizes to the costamere and remains there after α-catenin inactivation[217]. Experimental evidence also exists for a role of the striated muscle-specific protein, nebulin-related-anchoring protein (N-RAP), in myocyte mechanotransduction between the fascia adherens junction and the sarcomere[218,219].

Desmosomes connect intermediate filament cytoskeletal networks between cells and contain cadherins, desmocollin 2 and desmoglein 2. Mutations in these proteins are associated with arrhythmogenic right ventricular cardiomyopathy (ARVC)[209]. Desmoplakin connects desmosomes to the intermediate desmin filaments[209] in conjunction with desmosomal proteins junction plakoglobin (JUP) and plakophilin 2 (PKP2)[211]. A potential direct link between JUP and PKP2 in the cardiac muscle shear stress response has been shown[220]. Desmoplakin has been shown to be a critical component of the desmosome and cell–cell junctional integrity[221]; knocking out *Dsp* (encoding desmoplakin) causes sarcomeric defects and loss of desmosomal but not N-cadherin-based proteins and has been associated with ARVC[222]. Studies have suggested a role for desmosomes in transducing mechanical forces into multiple cellular responses related to tissue mechanics. Mutations in the desmosomal cadherins, desmocollin 2 and desmoglein 2 are linked to human ARVC[223].

Gap junctions are cell–cell connections that allow ions to pass between neighbouring cells, thereby electrically and metabolically connecting adjacent cells. Connexin 43 (also known as gap junction-α1 protein) is a gap junctional protein that is upregulated in response to mechanical stretch[224]. Upregulation of connexin 43 is accompanied by an increased number and size of gap junctions as well as by an accelerated conduction velocity[225]. Gap junctions are sensitive to mechanical stress[208] and remodel in several cardiac diseases. Crosstalk between adherens junctions, desmosomes and gap junction proteins, including α-catenin, tight junction protein ZO1, connexin 43 and PKP2, at the intercalated disc might account for the mechanisms of gap junction remodelling in cardiac disease[226].

Fibroblast–myocyte interactions.—Interactions between cardiac myocytes and fibroblasts can be via paracrine cell–cell signalling or via direct physical coupling between the different cell types, possibly mediated by the ECM. Fibroblasts can mediate myocardial electro-physiology via electrical coupling to myocytes and alterations in myocyte membrane potential and therefore electrical conduction[18,227–229]. Many fibroblast– myocyte interactions have been implicated in cardiac arrhythmogenesis[230–232]. Coupling between myocytes and fibroblasts can occur in vivo and represents electrotonic coupling between these different cell types[233,234]. Ongstad and colleagues suggest several ways in which cardiac myocytes and fibroblasts can couple to each other, including fibroblasts acting as insulators between myocytes or with small numbers of gap junctional channels that could serve as short-range or long-range conductions of electrical excitation[234]. Modifying hetero-typic cell–cell interactions and coupling might be useful in reducing arrhythmias after myocardial infarction[235]. Secreted factors such as angiotensin II, cardiotrophin 1, fibroblast growth factor, IL-6, insulin-like growth factor I, TGFβ and tumour necrosis factor have been shown to mediate cell–cell communication via indirect autocrine or paracrine mechanisms[236–238]. These factors regulate a host of physiological functions in the cells and tissue of the heart, most of which are described in the preceding sections involving signalling pathways related to development, electrical activity, contractile function and pathological tissue remodelling.

Systems-level cardiac mechanosignalling

As described in the previous section, a wide range of pathways have been implicated in mechanosensing. Appropriately, these studies have focused largely on gaining a more detailed understanding of particular mechanosensing mechanisms. However, as indicated in FIG. 1, how these mechanisms work in concert to mediate cardiac mechanoresponses is less understood. Global measurement and modelling approaches are complementing more mechanistically focused studies to progress towards a systems-level understanding of cardiac mechanosignalling.

Mechanosensitive gene expression

Heart.—Studies of gene expression downstream of individual mechanosensitive pathways have most often focused on the fetal gene programme or a small number of candidate genes in that particular pathway. By contrast, gene expression profiling using cDNA microarrays or RNA sequencing have allowed for a more comprehensive view of the transcriptome and discovery of mechano-sensitive gene programmes. Although the most prevalent causes of heart failure, including myocardial infarction and hypertension, have highly complex biochemical and mechanical perturbations that evolve slowly over time, studies of direct perturbations to myocardial mechanics have helped to inform which aspects are more closely associated with mechanosensing. Animal models of pressure overload by TAC, which induces concentric hypertrophy and interstitial fibrosis, have consistently demonstrated increased expression of natriuretic pep-tide genes, ECM-related genes (notably connective tissue growth factor and periostin) and cytoskeleton-related genes[239,240]. Knockout of *Nppa* further exacerbates the hypertrophic and fibrotic gene expression profiles caused by pressure overload[240]. Cardiac trans-criptomes from rats

subjected to pressure or volume overload identified consistent expression of *Nppa*, *Nppb*, *Mt1* (encoding metallothionein 1) and genes encoding proteins involved in mitochondrial metabolism or the cytoskeleton. Volume overload induced more distinct upregulation of genes encoding actin-binding proteins (such as tropomyosin 4 and thymosin-β4) and some ECM proteins (such as osteopontin)[241]. Volume overload and eccentric remodelling caused by mitral valve regurgitation is associated with increased expression of metalloproteinases and decreases in the expression of genes encoding non-collagen ECM proteins[242].

Several studies have characterized gene expression profiles from human failing hearts before and after mechanical unloading with an LVAD. Initial reports demonstrated that LVAD-induced reverse remodelling coincided with a decrease in the expression of genes associated with natriuretic peptides, ECM, sarcomeres, cytoskeleton and metabolism[243,244]. Subsequent studies, including comparisons with non-failing heart samples, demonstrated that LVAD-induced reverse structural remodelling does not similarly induce widespread reversal of gene expression but instead induces a distinct state[245–247]. In terms of functional responses related to gene expression, LVAD therapy has been shown, for example, to correlate with changes in calcium dynamics in cardiomyocytes[248]. Even in experiments and treatments involving direct mechanical intervention, the parallel effects on vascular remodelling, neuro-hormonal feedback and multiple cell types hinder the identification of genes whose expression is regulated directly by the mechanosensitivity of cardiac myocytes or fibroblasts.

Cardiac myocytes.—In the first transcriptomic measurements of stretched cardiac myocytes, Weinberg and colleagues found strongly mechanosensitive expression of *Il1rl1*, which encodes suppression of tumorigenicity 2 (ST2; also known as IL-1 receptor-like 1)[249]. After confirming mechanoregulated expression by traditional methods, they demonstrated increased levels of soluble ST2 protein after myocardial infarction in the serum of mice and humans[249]. Subsequently, ST2 has been developed substantially as a clinical biomarker and is approved by the FDA to predict outcomes from myocardial infarction and heart failure[250,251]. Frank and colleagues used microarrays to identify highly mechanoresponsive genes in rat stretched cultured cardiomyocytes, identifying *Gdf15* and *Hmox1* in addition to strong induction of the fetal gene programme and other previously reported stretch-responsive genes[252]. The investigators further demonstrated that stretch-responsive transcription of several genes could be blocked by angiotensin II receptor antagonists or mimicked by angiotensin II[252], thereby linking transcription to a known mechanotransduction pathway. McCain and colleagues used a novel stretching device with micropatterned membranes to control cardiac myocyte alignment, characterizing how the direction and duration of stretch affects the transcriptome[253]. Clustering of genes by expression pattern across conditions elucidated coordinated expression of genes associated with ECM and cytoskeletal remodelling as well as those previously associated with pathological hypertrophy or heart failure in vivo[253]. This study nicely illustrated how clustering of transcriptomic data from multiple treatment conditions and time points aids in the identification of coordinated gene expression programmes. A subsequent study in rat isolated ventricular myocytes subjected to cyclic stretch investigated gene expression at even more time points between 1 h and 48 h (REF.[254]). Detailed data on signalling and expression

time courses remain limited; however, as more studies on the sequences of signalling events become available, the data will provide new insight into which mechanisms are acting in parallel, which are dependent on upstream processes and which components of the network are sensors, transducers or effectors.

Fibroblasts—As an early application of cDNA micro-arrays, in 2001 Kessler and colleagues profiled the response of fibroblasts cultured in 3D collagen gels that were either mechanically restrained or unrestrained from cell-induced contraction[255]. Mechanical stress induced expression of many genes encoding proteins known to be related to focal adhesions, cytoskeletal remodelling and ECM, including those encoding collagen type I, MMP1 and connective tissue growth factor[255]. Driesen and colleagues demonstrated that spontaneous differentiation of cardiac fibroblasts on a rigid substrate could be prevented or even reversed by inhibition of TGFβ receptor type 1 (TGFβR1)[256]. Transcriptome profiling showed that compared with stiffness-induced myofibroblasts, TGFβR1-inhibited cells had lower expression of genes encoding proteins associated with fibrosis, adhesion and TGFβ signalling. By contrast, TGFβ-treated myofibroblasts had reduced expression of genes encoding proteins related to the cell cycle[256]. Alam and colleagues used RNA sequencing to identify how fibro-blast mechanosensitive gene expression and microRNAs are regulated by the LINC complex[206]. Disruption of the LINC complex by expressing a dominant-negative SUN domain-containing protein 1 (SUN1) caused increased expression of genes encoding proteins associated with ion transport, adhesion, motility and ECM organization on stiff but not soft substrates[206].

Studies of gene expression from cultured papillary muscles and engineered heart tissues have helped to bridge cellular and in vivo studies because these tissues are well suited for precise mechanical perturbations and contain multiple cardiac cell types. To elucidate transcriptomic responses to particular mechanical signals, Haggart and colleagues measured transcrip-tomic responses of contracting papillary muscles under combinations of physiological versus reduced myocyte shortening (as occurs with pressure overload) and mean stretch (as occurs with an LVAD)[257]. Reduced muscle shortening strongly regulated genes encoding proteins associated with the ECM and cardiomyocyte hypertrophy, partially overlapping with the gene expression seen with pressure overload in vivo. Hirt and colleagues found that engineered heart tissues with increased afterload developed hypertrophy and fibrosis consistent with that seen in pressure overload in vivo[258]. Transcriptome measurements demonstrated that increased afterload was associated with strong induction of genes associated with the fetal gene programme, ECM and glycolytic metabolism in a manner consistent with that seen with biochemically induced hypertrophy and in partial overlap with that seen with pressure overload in vivo[258]. Of note, in both papillary muscles[257] and engineered heart tissues[258], although only 10–15% of genes over-lapped with in vivo reports, the most highly responsive overlapping genes were associated with the fetal gene programme and the ECM.

TABLE 1 compares mechanoresponsive gene sets across animal models, human studies and cardiac cells. Individual genes that were noteworthy in each study are also listed. Nearly all studies showed significant expression of genes encoding protein related to the ECM, with the gene encoding connective tissue growth factor often being among the most

mechanoresponsive. Cardiac tissue or cardiac myocyte studies typically show increased expression of natriuretic peptides, consistent with their use as clinical biomarkers. Genes encoding focal adhesion proteins are also consistently responsive to stretch in cardiac myocytes and fibroblasts, whereas fibroblasts show additional expression of proliferation-related genes. Gene expression has been profiled with varying measurement technologies and analyses, which contributes to variation between studies in the consistency of reported gene sets. Cardiac myocyte cultures also contain non-myocytes, which might contribute to measured responses.

Regulation by microRNAs.—Gene expression is also substantially regulated at the post-transcriptional level by microRNAs, and some studies have begun to focus specifically on their role in response to mechanical stretch. MicroRNAs are short (~22-nucleotide), non-coding RNAs that bind complementary mRNAs to regulate mRNA degradation or protein translation. A large number of microRNAs are differentially expressed and control cardiac remodelling in vivo, as reviewed previously[259]. Microarrays were used to discover differentially expressed microRNAs in mice subjected to TAC-induced pressure overload or calcineurin overexpression, leading to identification of miR-195 as a regulator of cardiac hypertrophy[260]. To find microRNAs specifically responsive to cardiac myocyte stretch, Frey and colleagues used microarrays to identify eight stretch-responsive microRNAs[261]. Follow-up experiments identified miR-20a as being responsive to both stretch and simulated ischaemia–reperfusion, that overexpression of miR-20a was sufficient to protect cardiomyocytes from apoptosis and that expression of miR-20a was inversely correlated with pro-apoptotic miR-20a targets Egl nine homologue 3 and E2F family transcription factors[261]. Motivated by studies showing miR-208a regulation of cardiac hypertrophy[262,263], studies of cultured cardiac myocytes and myoblasts showed stretch-responsive TGFβ signalling that controlled miR-208a expression and either β-myosin heavy chain (also known as myosin 7) or collagen in the respective cell types[264,265]. Dynamics of mRNA and microRNA expression of stretched cardiac myocytes has also been examined by Rysa and colleagues, who predicted involvement of nuclear factor-like 2 and interferon regulatory transcription factors and let-7 family microRNAs[254].

Long (>200-nucleotide) intergenic non-coding RNAs[266] have also been shown to regulate cardiac remodelling[267] and more strongly correlate with reverse remodelling of human hearts after LVAD support[247]. Long non-coding RNAs have been shown to regulate the stretch response of vascular smooth muscle cells[268], but corresponding studies in stretched cardiac myocytes have not yet been reported.

Challenges of complexity

Despite a wealth of characterized mechanosensitive proteins, pathways and global transcriptional profiles, considerable knowledge gaps must be overcome to obtain a molecular systems-level understanding of how mechanical signals regulate gene expression and cardiac remodelling (BOX 1). Addressing these challenges of mechanosignalling complexity requires quantitative comparisons between combinations of mechanobio-chemical perturbations, measurements and experimental contexts. However, testing of all combinations is clearly not feasible and would overwhelm rather than provide new

conceptual insights. When closely integrated with experimental studies, mathematical systems models can provide rigorous frameworks for data integration, hypothesis generation, prioritization of experiments and understanding of complex systems269. In the following section, we provide an overview of how systems models have been applied to address complexity challenges for cardiac signalling networks, focusing on the latest work extending into mechanosignalling of cardiac myocytes and fibroblasts.

Systems models of mechanosignalling

Computational models of signalling and gene regulation in cardiac myocytes.

—Mathematical models have long provided crucial insights into how complex molecular systems regulate cardiac myocyte physiology[270]. Classic mathematical models provided insights into the molecular mechanisms of actin–myosin cross-bridge cycling[271] and feedback between ionic currents that drive cardiac pacemaking[272]. Over several decades, mathematical models have provided a wide range of systems-level insights into the molecular regulation of excitation–contraction coupling[273], arrhythmia[274], metabolism[275,276] and signalling pathways[277,278] in normal and pathological[279] conditions.

In contrast to the larger number of models of short-term (milliseconds to minutes) cardiac myocyte physiology, fewer models have examined the molecular networks that control longer-term gene expression and remodelling (hours to days)[269,280]. Tavi and colleagues used a model of calcium–calmodulin– calcineurin kinetics to show that calcineurin might act as a frequency-sensitive integrator of cytosolic calcium signals[281,282], which correlates with experimental measurements of NFAT activity, mRNA expression[281] and myocyte hypertrophy[283]. Other models coupled these systems to more detailed systems of upstream subcellular calcium dynamics[284] or mechanisms of NFAT nuclear transport[285]. Cooling and colleagues developed models of receptor-stimulated inositol 1,4,5-trisphosphate (IP3) transients that regulate calcium–calcineurin, showing that the distinct kinetics of transients could be explained by differences in the kinetics of endothelin and angiotensin II receptors[286]. Combining simulations and perturbation experiments, Shin and colleagues characterized crosstalk between calcineurin, PI3K and ERK pathways that produce a biphasic switching mechanism by which calcipressin 1 regulates calcineurin–NFAT activity[287]. Ryall and colleagues developed a systems model of the overall cardiac myocyte hyper-trophy signalling network, predicting RAS as an integrating network hub for many biochemical stimuli[288]. Their model also included a simplified integrin path-way that was sufficient to accurately predict stretch-responsive activation of three transcription factors and six hypertrophic genes[288]. This and other systems models were developed using data from cultured cardiac myocytes, whose relevance to in vivo hypertrophy has been debated[289,290]. To test the generalizability of this network model[288], overexpression of 34 genes was simulated and compared with in vivo data from cardiac-specific transgenic mice[291]. The model accurately predicted 72% of 168 in vivo measurements, as well as the hypertrophic phenotypes of four double-transgenic mice, with mis predictions guiding subsequent model revision on the basis of in vivo data[291].

Models linking mechanosignalling to cytoskeletal remodelling and gene expression.—

A number of mathematical models have provided insights into the

biophysical mechanisms that guide cytoskeletal remodelling, as reviewed previously[292]. Biophysical models have demonstrated how long stress fibres and heterogeneous distributions of focal adhesions in fibro-blasts arise from positive feedback between adhesion and stress fibre contractility[293], how further incorporation of cytoskeletal mechanics can predict regional orientation and density of stress fibres[294] and how cells re-orient in response to the direction of stretch[295]. Coupled biochemical–mechanical models have also been used to understand cardiac myocyte myofibre formation, accounting for differences from fibroblast stress fibres. Grosberg and colleagues accurately predicted myofibrillar patterning of geometrically constrained cardiac myocytes[296], which was driven by both fibre length– force dependence[293] and mutual alignment of myo-fibres due to parallel coupling[297]. Simulations by Yuan and colleagues predicted that cell–cell adhesion forces reduce local focal adhesion formation[298], helping cardiac myocytes to form a syncytium with aligned myofibrils, as found experimentally[299].

Systems-level models are further needed to provide insight into how mechanical cues are transduced and integrated into downstream signalling pathways and gene expression[269,292,300]. For example, discriminating the regulation by specific mechanical stimuli of particular signalling pathways is confounded by crosstalk and overlap between these different stimuli and downstream pathways. Several studies have illustrated the promise of such models to address challenges in mechanosignalling network integration.

Although studies of mechanosignalling have focused primarily on linear pathways from sensor to response, mechanoresponsiveness can also emerge from the interplay of more subtle relationships. Dingal and colleagues used a series of simplified models to illustrate how tension-inhibited protein degradation[301] (suchas is seen with many cardiac sarcomeric, cytoskeletal and matrix proteins[152,302]) coupled with positive regulation from protein to transcription can lead to tension-enhanced gene expression. Proteins such as lamin A with long protein half-lives but short mRNA half-lives were predicted to show steady, tension-enhanced mRNA and protein abundance, whereas proteins such as collagen with short protein half-lives were predicted to generate transient increases with stretch as seen experimentally. Coupling of mRNA–protein modules illustrated how tension-inhibited degradation of one protein might indirectly drive mechanoresponsive expression of other genes in a cytoskeletal network (for example, the effects of myosin 2 on lamin A) or coordinated gene expression in fibroblasts and cardiac myocytes[301].

Myofibroblast differentiation is highly responsive to mechanical signals as well as multiple growth factors, but the mechanisms underlying crosstalk between these signals are not well characterized. Schroer and colleagues developed a dynamic computational model of how integrin, TGFβ and fibroblast growth factor signals converge on p38 and ERK to coordinately regulate α-smooth muscle actin (αSMA) expression, a key marker of myofibroblasts[303]. Rather than using a single model, uncertainty regarding mechanisms involving SRC, ERK and p38 was addressed by comparing eight candidate models, each representing alternative hypotheses of the signalling network. Candidate networks incorporating SRC-dependent αSMA expression and SRC feedback provided the most parsimonious explanations for their experimentally observed responses to matrix stiffness, growth factors and genetic perturbations[303].

Mechanoresponsiveness of the transcriptional effectors YAP–TAZ has been shown to rely on cytoskeletal tension, non-muscle myosin and RhoA activity down-stream of integrins and cell adhesion[304]. Sun and colleagues developed a systems model integrating these mechanisms and crosstalk with cell–cell adhesion-sensitive Hippo pathway members, such as serine/ threonine-protein kinase LATS[305]. A strength of this model is that the equations were largely based on bio-physical mechanisms of cytoskeletal proteins and their biochemical regulation by signalling, effectively linking cytoskeletal regulation to signalling pathways. The model recapitulated a range of previously reported effects of perturbations on YAP–TAZ nuclear translocation[304], including inhibitors for myosin, RhoA, ROCK, F-actin and altered matrix stiffness[305]. The model was then used to make new predictions regarding increased mechanosensitivity of YAP–TAZ compared with SRF as well as synergistic regulation of YAP–TAZ by LATS[306] and RhoA pathways[305].

Large-scale systems models can integrate hetero-geneous datafrommanysources to identify network control principles. Zeigler and colleagues developed a systems model of the cardiac fibroblast signalling network, which integrated 11 biochemical or mechanical cues to regulate myofibroblast genes and ECM components in agreement with a wealth of independent literature[307]. Computational screening of network perturbations in multiple cell contexts predicted mechanoresponsive αSMA expression to require an autocrine loop with AP-1-dependent TGFβ expression and TGFβR1– SMAD3 signalling. Further simulations and validation experiments of fibroblasts in mechanically restrained collagen gels confirmed that TGFβR1 inhibition prevented αSMA expression[307]. These predictions were consistent with subsequent in vivo experiments by Khalil and colleagues showing that fibroblast-specific deletion of *Tgfbr1* and *Tgfbr2* or *Smad2* and *Smad3* suppressed cardiac fibrosis in response to pressure overload[308].

Despite the wide range of mechanosensitive pathways that have been identified, the systems models described above examined crosstalk between biochemical signals and only a single mechanosensor. To assess how cardio-myocytes integrate mechanical signals from multiple mechanosensitive proteins, Tan and colleagues reconstructed a cardiomyocyte mechanosignalling network model linking nine mechanoresponsive proteins (five shown to be directly responsive to stretch in reconstituted assays) to cardiomyocyte size, protein synthesis and eight mechanosensitive genes[309] (FIG. 2). Comparison of model predictions to independent published experiments yielded a validation rate of 78% (134 out of 172). Although the 11 transcription factors showed selective sensitivity to particular mechanosensors, functional cooperativity between transcription factors was predicted to make downstream genes more broadly sensitive. Computational perturbation screens predicted combinatorial ‘mechanotherapies’ that might suppress hyper-trophic gene expression, including combined stimulation of cGMP and inhibition of AT1R as might occur with the drug Entresto (Novartis; previous known as LCZ696, combining valsartan and sacubitril). The direct effects of Entresto on cardiomyocyte mechanosignalling have not yet been tested experimentally; however, in rats subjected to aortic constriction, Entresto suppressed cardiac expression of *Myh7* and *Nppa* and cardiomyocyte hypertrophy and increased expression of *Myh6* (REF.[310]) — all consistent with the previous model’s predictions[309]. Entresto has also been shown to attenuate cardiac hypertrophy after

myocardial infarction[311], in chronic kidney disease[312] and in angiotensin-II-stimulated cardiomyocytes[311].

Multiscale models of mechanoregulated ventricular growth and remodelling.—Ultimately, mathematical models will need to link predicted mechanotransduction mechanisms, signalling networks and gene expression to cardiac hypertrophy and myocardial tissue remodelling in response to haemodynamic changes and other alterations that affect myocardial mechanics. To date, progress has been made in organ-scale modelling of bio-mechanically stimulated growth and remodelling using empirical growth and remodelling laws[313]. Witzenburg and Holmes examined the capacity of several proposed hypertrophic growth laws to predict remodelling in response to pressure or volume overload[314]. Kerckhoffs and colleagues assumed that cardiomyocytes grow by adding sarcomeres in series when maximum fibre lengthening (that is, normally during filling) exceeds a homeostatic threshold and by adding sarcomeres in parallel when maximum cross-fibre strain (that is, typically during systole) exceeds a homeostatic threshold[315]. When the investigators implemented these rules in a 3D biomechanical model of the canine left and right ventricles coupled to haemodynamic models of the circulation, they found that the mechanical changes induced by simulated mitral valve regurgitation indeed predicted a pattern of eccentric ventricular hypertrophy consistent with experimental observations[316]. Similarly, the same growth rules under conditions of simulated aortic stenosis gave rise to a pattern of concentric hypertrophy similar to observations in canine experiments[317]. Multiscale models of extracellular remodelling by mechanically stimulated fibroblast activity have also been created. Rouillard and Holmes used a technique known as agentbased modelling to simulate collagen matrix synthesis and remodelling by fibroblasts in response to physicochemical stimuli and incorporated the multicellular model into a 3D model of post-infarction scar formation in the ventricular wall[318]. Taken together, these different modelling approaches provide the foundations for future, more mechanistic and integrated multiscale models that represent the biophysical mechanisms of cellular mechanotransduction of specific mechanical stimuli, the cell signalling pathways that integrate these responses, their downstream regulation of gene expression and phenotypic responses, the multicellular and tissue-scale changes in tissue structure and mechanical properties, and the feedback effects of these changes on the driving mechanical stimuli. Multiscale models could be particularly valuable for assessing potential thera-pies that combine pharmacological and device-based interventions.

Conclusions

A wide range of signalling pathways have been identified that mediate mechanosensing by cardiac myocytes and fibroblasts. The molecular responses to mechanical stimuli have also been profiled with increasing scope. However, the complexity of molecular networks has challenged attempts to understand more fully how particular mechanical signals are processed and integrated to control gene expression and cardiac remodelling. Systems models of mechanosignalling have begun to provide insights into how mechanical signals are integrated from multiple mechanosensors and crosstalk with biochemical stimuli to regulate fibroblast and cardiac myocyte gene expression. These models will need to be

closely integrated with extensive quantitative experiments that compare distinct mechanosignals and combinations of perturbations to mechanosensors and biochemical pathways. Such integrative systems analyses promise to integrate data across diverse experimental contexts, improve understanding of multiscale relationships and accelerate the development of therapeutics that control how mechanical stimuli remodel the heart.

Acknowledgements

The authors acknowledge the following funding sources: US National Science Foundation grant 1252854 (J.J.S.); NIH grants R01 HL137755 (J.J.S.), R01 HL137100 (A.D.M.) and U01 HL127564; and US Department of Defense PR 150090 (supporting J.H.O.).

A.D.M. and J.H.O. are co-founders of and have an equity interest in Insilicomed, and A.D.M. has an equity interest in Vektor Medical. A. D.M. and J. H. O. serve on the scientific advisory board of Insilicomed, and A.D.M. is a scientific adviser to both companies. Some of their research grants have been identified for conflict of interest management on the basis of the overall scope of the project and its potential benefit to these companies. The authors are required to disclose this relationship in publications acknowledging the grant support; however, the research subject and findings reported in this Review did not involve the companies in any way and have no specific relationship with the business activities or scientific interests of either company. The terms of this arrangement have been reviewed and approved by the University of California San Diego in accordance with its conflict of interest policies.

References

1. Azevedo PS, Polegato BF, Minicucci MF, Paiva SAR & Zornoff LAM Cardiac remodeling: concepts, clinical impact, pathophysiological mechanisms and pharmacologic treatment. Arq. Bras. Cardiol 106, 62–69 (2016). [PubMed: 26647721]
2. Mann DL Left ventricular size and shape: determinants of mechanical signal transduction pathways. Heart Fail. Rev 10, 95–100 (2005). [PubMed: 16258716]
3. Swynghedauw B Darwinian evolution and cardiovascular remodeling. Heart Fail. Rev 21, 795–802 (2016). [PubMed: 27440137]
4. Chiquet M, Gelman L, Lutz R & Maier S From mechanotransduction to extracellular matrix gene expression in fibroblasts. Biochim. Biophys. Acta 1793, 911–920 (2009). [PubMed: 19339214]
5. Barry SP, Davidson SM & Townsend PA Molecular regulation of cardiac hypertrophy. Int. J. Biochem. Cell Biol 40, 2023–2039 (2008). [PubMed: 18407781]
6. Ruwhof C & van der Laarse A Mechanical stress-induced cardiac hypertrophy: mechanisms and signal transduction pathways. Cardiovasc. Res 47, 23–37 (2000). [PubMed: 10869527]
7. Russell B, Motlagh D & Ashley WW Form follows function: how muscle shape is regulated by work. J. Appl. Physiol 88, 1127–1132 (2000). [PubMed: 10710412]
8. Braunwald E Heart failure. JACC Heart Fail 1, 1–20 (2013). [PubMed: 24621794]
9. Rohini A, Agrawal N, Koyani CN & Singh R Molecular targets and regulators of cardiac hypertrophy. Pharmacol. Res 61, 269–280 (2010). [PubMed: 19969085]
10. Douglas PS, Morrow R, Ioli A & Reichek N Left ventricular shape, afterload and survival in idiopathic dilated cardiomyopathy. J. Am. Coll. Cardiol 13, 311–315 (1989). [PubMed: 2913109]
11. Gupta S, Das B & Sen S Cardiac hypertrophy: mechanisms and therapeutic opportunities. Antioxid. Redox Signal 9, 623–652 (2007). [PubMed: 17511580]
12. Topkara VK et al. Myocardial recovery in patients receiving contemporary left ventricular assist devices: results from the interagency registry for mechanically assisted circulatory support (INTERMACS). Circ. Heart Fail 9, e003157 (2016). [PubMed: 27402861]
13. Heerdt PM et al. Chronic unloading by left ventricular assist device reverses contractile dysfunction and alters gene expression in end-stage heart failure. Circulation 102, 2713–2719 (2000). [PubMed: 11094037]
14. Pinto AR et al. Revisiting cardiac cellular composition. Circ. Res 118, 400–409 (2016). [PubMed: 26635390]

15. Humphrey JD, Dufresne ER & Schwartz MA Mechanotransduction and extracellular matrix homeostasis. Nat. Rev. Mol. Cell Biol 15, 802–812 (2014). [PubMed: 25355505]
16. Lyon RC, Zanella F, Omens JH & Sheikh F Mechanotransduction in cardiac hypertrophy and failure. Circ. Res 116, 1462–1476 (2015). [PubMed: 25858069]
17. Herum KM, Lunde IG, McCulloch AD & Christensen G The soft- and hard-heartedness of cardiac fibroblasts: mechanotransduction signaling pathways in fibrosis of the heart. J. Clin. Med 6, E53 (2017). [PubMed: 28534817]
18. Zeigler AC, Richardson WJ, Holmes JW & Saucerman JJ Computational modeling of cardiac fibroblasts and fibrosis. J. Mol. Cell. Cardiol 93, 73–83 (2016). [PubMed: 26608708]
19. Civitarese RA, Kapus A, McCulloch CA & Connelly KA Role of integrins in mediating cardiac fibroblast-cardiomyocyte cross talk: a dynamic relationship in cardiac biology and pathophysiology. Bas. Res. Cardiol 112, 6 (2017).
20. Park JY et al. Comparative analysis of mRNA isoform expression in cardiac hypertrophy and development reveals multiple post-transcriptional regulatory modules. PLOS ONE 6, e22391 (2011). [PubMed: 21799842]
21. Wang JH, Thampatty BP, Lin JS & Im HJ Mechanoregulation of gene expression in fibroblasts. Gene 391, 1–15 (2007). [PubMed: 17331678]
22. Lichter JG et al. Remodeling of the sarcomeric cytoskeleton in cardiac ventricular myocytes during heart failure and after cardiac resynchronization therapy. J. Mol. Cell. Cardiol 72, 186–195 (2014). [PubMed: 24657727]
23. Haque ZK & Wang DZ How cardiomyocytes sense pathophysiological stresses for cardiac remodeling. Cell. Mol. Life Sci 74, 983–1000 (2017). [PubMed: 27714411]
24. Davis J et al. A tension-based model distinguishes hypertrophic versus dilated cardiomyopathy. Cell 165, 1147–1159 (2016). [PubMed: 27114035]
25. Plitt GD, Spring JT, Moulton MJ & Agrawal DK Mechanisms, diagnosis, and treatment of heart failure with preserved ejection fraction and diastolic dysfunction. Expert Rev. Cardiovasc. Ther 16, 579–589 (2018). [PubMed: 29976104]
26. Kassi M, Hannawi B & Trachtenberg B Recent advances in heart failure. Curr. Opin. Cardiol 33, 249–256 (2018). [PubMed: 29300199]
27. Zhou P & Pu WT Recounting cardiac cellular composition. Circ. Res 118, 368–370 (2016). [PubMed: 26846633]
28. Carter WG, Wayner EA, Bouchard TS & Kaur P The role of integrins alpha 2 beta 1 and alpha 3 beta 1 in cell-cell and cell-substrate adhesion of human epidermal cells. J. Cell Biol 110, 1387–1404 (1990). [PubMed: 1691191]
29. Babbitt CJ, Shai SY, Harpf AE, Pham CG & Ross RS Modulation of integrins and integrin signaling molecules in the pressure-loaded murine ventricle. Histochem. Cell Biol 118, 431–439 (2002). [PubMed: 12483308]
30. Li R et al. beta1 integrin gene excision in the adult murine cardiac myocyte causes defective mechanical and signaling responses. Am. J. Pathol 180, 952–962 (2012). [PubMed: 22248583]
31. Traister A et al. Integrin-linked kinase mediates force transduction in cardiomyocytes by modulating SERCA2a/PLN function. Nat. Commun 5, 4533 (2014). [PubMed: 25208486]
32. Kostin S et al. The internal and external protein scaffold of the T-tubular system in cardiomyocytes. Cell Tissue Res 294, 449–460 (1998). [PubMed: 9799462]
33. Wang N, Butler JP & Ingber DE Mechanotransduction across the cell surface and through the cytoskeleton. Science 260, 1124–1127 (1993). [PubMed: 7684161]
34. Kuppuswamy D et al. Association of tyrosine-phosphorylated c-Src with the cytoskeleton of hypertrophying myocardium. J. Biol. Chem 272, 4500–4508 (1997). [PubMed: 9020175]
35. Zhang SJ, Truskey GA & Kraus WE Effect of cyclic stretch on beta1D-integrin expression and activation of FAK and RhoA. Am. J. Physiol. Cell Physiol 292, C2057–C2069 (2007). [PubMed: 17267546]
36. Israeli-Rosenberg S, Manso AM, Okada H & Ross RS Integrins and integrin-associated proteins in the cardiac myocyte. Circ. Res 114, 572–586 (2014). [PubMed: 24481847]

37. Zemljic-Harpf AE et al. Heterozygous inactivation of the vinculin gene predisposes to stress-induced cardiomyopathy. Am. J. Pathol 165, 1033–1044 (2004). [PubMed: 15331426]
38. Manso AM et al. Talin1 has unique expression versus talin 2 in the heart and modifies the hypertrophic response to pressure overload. J. Biol. Chem 288, 4252–4264 (2013). [PubMed: 23266827]
39. Critchley DR Biochemical and structural properties of the integrin-associated cytoskeletal protein talin. Annu. Rev. Biophys 38, 235–254 (2009). [PubMed: 19416068]
40. Kovacic-Milivojevic B et al. Focal adhesion kinase and p130Cas mediate both sarcomeric organization and activation of genes associated with cardiac myocyte hypertrophy. Mol. Biol. Cell 12, 2290–2307 (2001). [PubMed: 11514617]
41. Pham CG et al. Striated muscle-specific beta(1D)-integrin and FAK are involved in cardiac myocyte hypertrophic response pathway. Am. J. Physiol. Heart Circ. Physiol 279, H2916–H2926 (2000). [PubMed: 11087248]
42. Travers JG, Kamal FA, Robbins J, Yutzey KE & Blaxall BC Cardiac fibrosis: the fibroblast awakens. Circ. Res 118, 1021–1040 (2016). [PubMed: 26987915]
43. Kim SH, Turnbull J & Guimond S Extracellular matrix and cell signalling: the dynamic cooperation of integrin, proteoglycan and growth factor receptor. J. Endocrinol 209, 139–151 (2011). [PubMed: 21307119]
44. MacKenna D, Summerour SR & Villarreal FJ Role of mechanical factors in modulating cardiac fibroblast function and extracellular matrix synthesis. Cardiovasc. Res 46, 257–263 (2000). [PubMed: 10773229]
45. Zaidel-Bar R, Itzkovitz S, Ma'ayan A, Iyengar R & Geiger B Functional atlas of the integrin adhesome. Nat. Cell Biol 9, 858–867 (2007). [PubMed: 17671451]
46. Teoh CM, Tam JK & Tran T Integrin and GPCR crosstalk in the regulation of ASM contraction signaling in asthma. J. Allergy 2012, 341282 (2012).
47. Margadant C & Sonnenberg A Integrin-TGF-beta crosstalk in fibrosis, cancer and wound healing. EMBO Rep 11, 97–105 (2010). [PubMed: 20075988]
48. MacKenna DA, Dolfi F, Vuori K & Ruoslahti E Extracellular signal-regulated kinase and c-Jun NH2-terminal kinase activation by mechanical stretch is integrin-dependent and matrix-specific in rat cardiac fibroblasts. J. Clin. Invest 101, 301–310 (1998). [PubMed: 9435301]
49. Herum KM, Choppe J, Kumar A, Engler AJ & McCulloch AD Mechanical regulation of cardiac fibroblast profibrotic phenotypes. Mol. Biol. Cell 28, 1871–1882 (2017). [PubMed: 28468977]
50. Seong J et al. Distinct biophysical mechanisms of focal adhesion kinase mechanoactivation by different extracellular matrix proteins. Proc. Natl Acad. Sci. USA 110, 19372–19377 (2013). [PubMed: 24222685]
51. Hynes RO Integrins: bidirectional, allosteric signaling machines. Cell 110, 673–687 (2002). [PubMed: 12297042]
52. Davis J & Molkentin JD Myofibroblasts: trust your heart and let fate decide. J. Mol. Cell. Cardiol 70, 9–18 (2014). [PubMed: 24189039]
53. Molkentin JD et al. Fibroblast-specific genetic manipulation of p38 mitogen-activated protein kinase in vivo reveals its central regulatory role in fibrosis. Circulation 136, 549–561 (2017). [PubMed: 28356446]
54. Lapidos KA, Kakkar R & McNally EM The dystrophin glycoprotein complex: signaling strength and integrity for the sarcolemma. Circ. Res 94, 1023–1031 (2004). [PubMed: 15117830]
55. Jung D, Yang B, Meyer J, Chamberlain JS & Campbell KP Identification and characterization of the dystrophin anchoring site on beta-dystroglycan. J. Biol. Chem 270, 27305–27310 (1995). [PubMed: 7592992]
56. Ervasti JM & Campbell KP Dystrophin-associated glycoproteins: their possible roles in the pathogenesis of Duchenne muscular dystrophy. Mol. Cell Biol. Hum. Dis. Ser 3, 139–166 (1993). [PubMed: 8111538]
57. Emery AE Duchenne muscular dystrophy—Meryon's disease. Neuromuscul. Disord 3, 263–266 (1993). [PubMed: 8268722]

58. Towbin JA et al. X-Linked dilated cardiomyopathy. Molecular genetic evidence of linkage to the Duchenne muscular dystrophy (dystrophin) gene at the Xp21 locus. Circulation 87, 1854–1865 (1993). [PubMed: 8504498]
59. Lynch GS, Hinkle RT, Chamberlain JS, Brooks SV & Faulkner JA Force and power output of fast and slow skeletal muscles from mdx mice 6–28 months old. J. Physiol 535, 591–600 (2001). [PubMed: 11533147]
60. Barnabei MS & Metzger JM Ex vivo stretch reveals altered mechanical properties of isolated dystrophin-deficient hearts. PLOS ONE 7, e32880 (2012). [PubMed: 22427904]
61. Garbincius JF & Michele DE Dystrophin-glycoprotein complex regulates muscle nitric oxide production through mechanoregulation of AMPK signaling. Proc. Natl Acad. Sci. USA 112, 13663–13668 (2015). [PubMed: 26483453]
62. Porter JD et al. A chronic inflammatory response dominates the skeletal muscle molecular signature in dystrophin-deficient mdx mice. Hum. Mol. Genet 11, 263–272 (2002). [PubMed: 11823445]
63. Chen YW, Zhao P, Borup R & Hoffman EP Expression profiling in the muscular dystrophies: identification of novel aspects of molecular pathophysiology. J. Cell Biol 151, 1321–1336 (2000). [PubMed: 11121445]
64. Reed A, Kohl P & Peyronnet R Molecular candidates for cardiac stretch-activated ion channels. Glob. Cardiol. Sci. Pract 2014, 9–25 (2014). [PubMed: 25405172]
65. Komuro I et al. Mechanical stretch activates the stress-activated protein kinases in cardiac myocytes. FASEB J 10, 631–636 (1996). [PubMed: 8621062]
66. Sadoshima J & Izumo S Mechanical stretch rapidly activates multiple signal transduction pathways in cardiac myocytes: potential involvement of an autocrine/paracrine mechanism. EMBO J 12, 1681–1692 (1993). [PubMed: 8385610]
67. Sigurdson W, Ruknudin A & Sachs F Calcium imaging of mechanically induced fluxes in tissue-cultured chick heart: role of stretch-activated ion channels. Am. J. Physiol 262, H1110–H1115 (1992). [PubMed: 1373571]
68. Lyford GL et al. alpha(1C) (Ca(V)1.2) L-type calcium channel mediates mechanosensitive calcium regulation. Am. J. Physiol. Cell Physiol 283, C1001–1008 (2002). [PubMed: 12176756]
69. Peng S-Q, Hajela RK & Atchison WD Fluid flow-induced increase in inward Ba^{2+} current expressed in HEK293 cells transiently transfected with human neuronal L-type Ca^{2+} channels. Brain Res 1045, 116–123 (2005). [PubMed: 15910769]
70. Rosa AO, Yamaguchi N & Morad M Mechanical regulation of native and the recombinant calcium channel. Cell Calcium 53, 264–274 (2013). [PubMed: 23357406]
71. Katanosaka Y et al. TRPV2 is critical for the maintenance of cardiac structure and function in mice. Nat. Commun 5, 3932 (2014). [PubMed: 24874017]
72. Teng J, Loukin S, Zhou X & Kung C Yeast luminometric and Xenopus oocyte electrophysiological examinations of the molecular mechanosensitivity of TRPV4. J. Vis. Exp 82, 50816 (2013).
73. Qi Y et al. Uniaxial cyclic stretch stimulates TRPV4 to induce realignment of human embryonic stem cell-derived cardiomyocytes. J. Mol. Cell. Cardiol 87, 65–73 (2015). [PubMed: 26259779]
74. Cadre BM et al. Cyclic stretch down-regulates calcium transporter gene expression in neonatal rat ventricular myocytes. J. Mol. Cell. Cardiol 30, 2247–2259 (1998). [PubMed: 9925362]
75. Jeong D et al. PICOT attenuates cardiac hypertrophy by disrupting calcineurin-NFAT signaling. Circ. Res 102, 711–719 (2008). [PubMed: 18258855]
76. Finsen AV et al. Syndecan-4 is essential for development of concentric myocardial hypertrophy via stretch-induced activation of the calcineurin-NFAT pathway. PLOS ONE 6, e28302 (2011). [PubMed: 22164265]
77. Peyronnet R, Nerbonne JM & Kohl P Cardiac mechano-gated ion channels and arrhythmias. Circ. Res 118, 311–329 (2016). [PubMed: 26838316]
78. Striessnig J, Ortner NJ & Pinggera A Pharmacology of L-type calcium channels: novel drugs for old targets? Curr. Mol. Pharmacol 8, 110–122 (2015). [PubMed: 25966690]
79. Rog-Zielinska EA, Norris RA, Kohl P & Markwald R The living scar — cardiac fibroblasts and the injured heart. Trends Mol. Med 22, 99–114 (2016). [PubMed: 26776094]

80. Kamkin A, Kiseleva I & Isenberg G Activation and inactivation of a non-selective cation conductance by local mechanical deformation of acutely isolated cardiac fibroblasts. Cardiovasc. Res 57, 793–803 (2003). [PubMed: 12618241]
81. Kamkin A et al. Cardiac fibroblasts and the mechano-electric feedback mechanism in healthy and diseased hearts. Prog. Biophys. Mol. Biol 82, 111–120 (2003). [PubMed: 12732272]
82. Numaga-Tomita T et al. TRPC3-GEF-H1 axis mediates pressure overload-induced cardiac fibrosis. Sci. Rep 6, 39383 (2016). [PubMed: 27991560]
83. Sharma S et al. TRPV4 ion channel is a novel regulator of dermal myofibroblast differentiation. Am. J. Physiol. Cell Physiol 312, C562–C572 (2017). [PubMed: 28249987]
84. Adapala RK et al. TRPV4 channels mediate cardiac fibroblast differentiation by integrating mechanical and soluble signals. J. Mol. Cell. Cardiol 54, 45–52 (2013). [PubMed: 23142541]
85. Bers DM Calcium cycling and signaling in cardiac myocytes. Annu. Rev. Physiol 70, 23–49 (2008). [PubMed: 17988210]
86. Chen-Izu Y & Izu LT Mechano-chemo-transduction in cardiac myocytes. J. Physiol 595, 3949–3958 (2017). [PubMed: 28098356]
87. Ruwhof C et al. Mechanical stress stimulates phospholipase C activity and intracellular calcium ion levels in neonatal rat cardiomyocytes. Cell Calcium 29, 73–83 (2001). [PubMed: 11162845]
88. Gerdes AM & Capasso JM Structural remodeling and mechanical dysfunction of cardiac myocytes in heart failure. J. Mol. Cell. Cardiol 27, 849–856 (1995). [PubMed: 7602601]
89. Iribe G et al. Axial stretch of rat single ventricular cardiomyocytes causes an acute and transient increase in Ca^{2+} spark rate. Circ. Res 104, 787–795 (2009). [PubMed: 19197074]
90. Limbu S, Hoang-Trong TM, Prosser BL, Lederer WJ & Jafri MS Modeling local X-ROS and calcium signaling in the heart. Biophys. J 109, 2037–2050 (2015). [PubMed: 26588563]
91. Prosser BL, Ward CW & Lederer WJ X-ROS signaling: rapid mechano-chemo transduction in heart. Science 333, 1440–1445 (2011). [PubMed: 21903813]
92. Allen DG & Kentish JC The cellular basis of the length-tension relation in cardiac muscle. J. Mol. Cell. Cardiol 17, 821–840 (1985). [PubMed: 3900426]
93. Kurihara S & Komukai K Tension-dependent changes of the intracellular Ca^{2+} transients in ferret ventricular muscles. J. Physiol 489, 617–625 (1995). [PubMed: 8788928]
94. Morad M, Javaheri A, Risius T & Belmonte S Multimodality of Ca^{2+} signaling in rat atrial myocytes. Ann. NY Acad. Sci 1047, 112–121 (2005). [PubMed: 16093489]
95. Gruver CL, DeMayo F, Goldstein MA & Means AR Targeted developmental overexpression of calmodulin induces proliferative and hypertrophic growth of cardiomyocytes in transgenic mice. Endocrinology 133, 376–388 (1993). [PubMed: 8319584]
96. Zhang CL et al. Class II histone deacetylases act as signal-responsive repressors of cardiac hypertrophy. Cell 110, 479–488 (2002). [PubMed: 12202037]
97. Linseman DA et al. Inactivation of the myocyte enhancer factor-2 repressor histone deacetylase-5 by endogenous Ca(2 +) //calmodulin-dependent kinase II promotes depolarization-mediated cerebellar granule neuron survival. J. Biol. Chem 278, 41472–41481 (2003). [PubMed: 12896970]
98. Dolmetsch RE, Lewis RS, Goodnow CC & Healy JI Differential activation of transcription factors induced by Ca^{2+} response amplitude and duration. Nature 386, 855–858 (1997). [PubMed: 9126747]
99. Molkentin JD Calcineurin-NFAT signaling regulates the cardiac hypertrophic response in coordination with the MAPKs. Cardiovasc. Res 63, 467–475 (2004). [PubMed: 15276472]
100. Zobel C et al. Mechanisms of Ca^{2+}-dependent calcineurin activation in mechanical stretch-induced hypertrophy. Cardiology 107, 281–290 (2007). [PubMed: 17264507]
101. Wu Z, Wong K, Glogauer M, Ellen RP & McCulloch CA Regulation of stretch-activated intracellular calcium transients by actin filaments. Biochem. Biophys. Res. Commun 261, 419–425 (1999). [PubMed: 10425200]
102. Rosen LB & Greenberg ME Stimulation of growth factor receptor signal transduction by activation of voltage-sensitive calcium channels. Proc. Natl Acad. Sci. USA 93, 1113–1118 (1996). [PubMed: 8577724]

103. Iqbal J & Zaidi M Molecular regulation of mechanotransduction. Biochem. Biophys. Res. Commun 328, 751–755 (2005). [PubMed: 15694410]
104. Davis J, Burr AR, Davis GF, Birnbaumer L & Molkentin JDA TRPC6-dependent pathway for myofibroblast transdifferentiation and wound healing in vivo. Dev. Cell 23, 705–715 (2012). [PubMed: 23022034]
105. De Mello WC & Danser AH Angiotensin II and the heart: on the intracrine renin-angiotensin system. Hypertension 35, 1183–1188 (2000). [PubMed: 10856260]
106. Leenen FH, Skarda V, Yuan B & White R Changes in cardiac ANG II postmyocardial infarction in rats: effects of nephrectomy and ACE inhibitors. Am. J. Physiol 276, H317–H325 (1999). [PubMed: 9887046]
107. Sadoshima J, Xu Y, Slayter HS & Izumo S Autocrine release of angiotensin II mediates stretch-induced hypertrophy of cardiac myocytes in vitro. Cell 75, 977–984 (1993). [PubMed: 8252633]
108. Miyata S, Haneda T, Osaki J & Kikuchi K Renin-angiotensin system in stretch-induced hypertrophy of cultured neonatal rat heart cells. Eur. J. Pharmacol 307, 81–88 (1996). [PubMed: 8831108]
109. Rosenkranz S TGF-beta1 and angiotensin networking in cardiac remodeling. Cardiovasc. Res 63, 423–432 (2004). [PubMed: 15276467]
110. Yamazaki T, Komuro I & Yazaki Y Molecular aspects of mechanical stress-induced cardiac hypertrophy. Mol. Cell. Biochem 163, 197–201 (1996). [PubMed: 8974057]
111. Aikawa R et al. Rho family small G proteins play critical roles in mechanical stress-induced hypertrophic responses in cardiac myocytes. Circ. Res 84, 458–466 (1999). [PubMed: 10066681]
112. McWhinney CD, Hunt RA, Conrad KM, Dostal DE & Baker KM The type I angiotensin II receptor couples to Stat1 and Stat3 activation through Jak2 kinase in neonatal rat cardiac myocytes. J. Mol. Cell. Cardiol 29, 2513–2524 (1997). [PubMed: 9299374]
113. Pan J et al. Mechanical stretch activates the JAK/ STAT pathway in rat cardiomyocytes. Circ. Res 84, 1127–1136 (1999). [PubMed: 10347087]
114. van Wamel AJ, Ruwhof C, van der Valk-Kokshoom LE, Schrier PI & van der Laarse A The role of angiotensin II, endothelin-1 and transforming growth factor-beta as autocrine/paracrine mediators of stretch-induced cardiomyocyte hypertrophy. Mol. Cell. Biochem 218, 113–124 (2001). [PubMed: 11330825]
115. Wang TL, Yang YH, Chang H & Hung CR Angiotensin II signals mechanical stretch-induced cardiac matrix metalloproteinase expression via JAK-STAT pathway. J. Mol. Cell. Cardiol 37, 785–794 (2004). [PubMed: 15350851]
116. Zou Y et al. Mechanical stress activates angiotensin II type 1 receptor without the involvement of angiotensin II. Nat. Cell Biol 6, 499–506 (2004). [PubMed: 15146194]
117. Rakesh K et al. beta-Arrestin-biased agonism of the angiotensin receptor induced by mechanical stress. Sci. Signal 3, ra46 (2010). [PubMed: 20530803]
118. Tang W, Strachan RT, Lefkowitz RJ & Rockman HA Allosteric modulation of β-arrestin-biased angiotensin II type 1 receptor signalling by membrane stretch. J. Biol. Chem 289, 28271–28283 (2014). [PubMed: 25170081]
119. Jiang G et al. Identification of amino acid residues in angiotensin II type 1 receptor sensing mechanical stretch and function in cardiomyocyte hypertrophy. Cell. Physiol. Biochem 37, 105–116 (2015). [PubMed: 26303226]
120. Abraham DM et al. β-arrestin mediates the Frank-Starling mechanism of cardiac contractility. Proc. Natl Acad. Sci. USA 113, 14426–14431 (2016). [PubMed: 27911784]
121. Leri A et al. Stretch-mediated release of angiotensin II induces myocyte apoptosis by activating p53 that enhances the local renin-angiotensin system and decreases the Bcl-2-to-Bax protein ratio in the cell. J. Clin. Invest 101, 1326–1342 (1998). [PubMed: 9525975]
122. Shyu KG, Chen CC, Wang BW & Kuan P Angiotensin II receptor antagonist blocks the expression of connexin43 induced by cyclical mechanical stretch in cultured neonatal rat cardiac myocytes. J. Mol. Cell. Cardiol 33, 691–698 (2001). [PubMed: 11273722]
123. Zablocki D & Sadoshima J Solving the cardiac hypertrophy riddle: The angiotensin II-mechanical stress connection. Circ. Res 113, 1192–1195 (2013). [PubMed: 24201113]

124. von Lueder TG & Krum H RAAS inhibitors and cardiovascular protection in large scale trials. Cardiovasc. Drugs Ther 27, 171–179 (2013). [PubMed: 23224653]
125. Porter KE & Turner NA Cardiac fibroblasts: at the heart of myocardial remodeling. Pharmacol. Ther 123, 255–278 (2009). [PubMed: 19460403]
126. Weber KT Fibrosis in hypertensive heart disease: focus on cardiac fibroblasts. J. Hypertens 22, 47–50 (2004). [PubMed: 15106793]
127. Staufenberger S et al. Angiotensin II type 1 receptor regulation and differential trophic effects on rat cardiac myofibroblasts after acute myocardial infarction. J. Cell. Physiol 187, 326–335 (2001). [PubMed: 11319756]
128. Sun Y, Zhang JQ, Zhang J & Ramires FJ Angiotensin II, transforming growth factor-beta1 and repair in the infarcted heart. J. Mol. Cell. Cardiol 30, 1559–1569 (1998). [PubMed: 9737942]
129. Lee AA, Dillmann WH, McCulloch AD & Villarreal FJ Angiotensin II stimulates the autocrine production of transforming growth factor-beta 1 in adult rat cardiac fibroblasts. J. Mol. Cell. Cardiol 27, 2347–2357 (1995). [PubMed: 8576949]
130. Gray MO, Long CS, Kalinyak JE, Li HT & Karliner JS Angiotensin II stimulates cardiac myocyte hypertrophy via paracrine release of TGF-beta 1 and endothelin-1 from fibroblasts. Cardiovasc. Res 40, 352–363 (1998). [PubMed: 9893729]
131. Campbell SE & Katwa LC Angiotensin II stimulated expression of transforming growth factor-beta1 in cardiac fibroblasts and myofibroblasts. J. Mol. Cell. Cardiol 29, 1947–1958 (1997). [PubMed: 9236148]
132. Pan CH, Wen CH & Lin CS Interplay of angiotensin II and angiotensin(1–7) in the regulation of matrix metalloproteinases of human cardiocytes. Exp. Physiol 93, 599–612 (2008). [PubMed: 18296491]
133. Lijnen P, Petrov V, van Pelt J & Fagard R Inhibition of superoxide dismutase induces collagen production in cardiac fibroblasts. Am. J. Hypertens 21, 1129–1136 (2008). [PubMed: 18756259]
134. Sano M et al. ERK and p38 MAPK, but not NF-kappaB, are critically involved in reactive oxygen species-mediated induction of IL-6 by angiotensin II in cardiac fibroblasts. Circ. Res 89, 661–669 (2001). [PubMed: 11597988]
135. Yokoyama T et al. Angiotensin II and mechanical stretch induce production of tumor necrosis factor in cardiac fibroblasts. Am. J. Physiol 276, H1968–H1976 (1999). [PubMed: 10362677]
136. Olson ER, Naugle JE, Zhang X, Bomser JA & Meszaros JG Inhibition of cardiac fibroblast proliferation and myofibroblast differentiation by resveratrol. Am. J. Physiol. Heart Circ. Physiol 288, H1131–H1138 (2005). [PubMed: 15498824]
137. Bouzegrhane F & Thibault G Is angiotensin II a proliferative factor of cardiac fibroblasts? Cardiovasc. Res 53, 304–312 (2002). [PubMed: 11827680]
138. Chintalgattu V, Harris GS, Akula SM & Katwa LC PPAR-gamma agonists induce the expression of VEGF and its receptors in cultured cardiac myofibroblasts. Cardiovasc. Res 74, 140–150 (2007). [PubMed: 17320065]
139. Chao HH et al. Inhibition of angiotensin II induced endothelin-1 gene expression by 17-beta-oestradiol in rat cardiac fibroblasts. Heart 91, 664–669 (2005). [PubMed: 15831659]
140. Pauschinger M et al. Dilated cardiomyopathy is associated with significant changes in collagen type I/III ratio. Circulation 99, 2750–2756 (1999). [PubMed: 10351968]
141. Li RK et al. Overexpression of transforming growth factor-beta1 and insulin-like growth factor-I in patients with idiopathic hypertrophic cardiomyopathy. Circulation 96, 874–881 (1997). [PubMed: 9264495]
142. Wenzel S, Taimor G, Piper HM & Schluter KD Redox-sensitive intermediates mediate angiotensin II-induced p38 MAP kinase activation, AP-1 binding activity, and TGF-beta expression in adult ventricular cardiomyocytes. FASEB J 15, 2291–2293 (2001). [PubMed: 11511516]
143. Brand T & Schneider MD The TGF beta superfamily in myocardium: ligands, receptors, transduction, and function. J. Mol. Cell. Cardiol 27, 5–18 (1995). [PubMed: 7760369]
144. Parker TG, Packer SE & Schneider MD Peptide growth factors can provoke “fetal” contractile protein gene expression in rat cardiac myocytes. J. Clin. Invest 85, 507–514 (1990). [PubMed: 1688886]

145. Koitabashi N et al. Pivotal role of cardiomyocyte TGF-beta signaling in the murine pathological response to sustained pressure overload. J. Clin. Invest 121, 2301–2312 (2011). [PubMed: 21537080]

146. Banerjee I et al. Cyclic stretch of embryonic cardiomyocytes increases proliferation, growth, and expression while repressing TGF-β signaling. J. Mol. Cell. Cardiol 79, 133–144 (2015). [PubMed: 25446186]

147. Frangogiannis NG The role of transforming growth factor (TGF)-beta in the infarcted myocardium. J. Thorac. Dis 9, S52–S63 (2017). [PubMed: 28446968]

148. Biernacka A, Dobaczewski M & Frangogiannis NG TGF-beta signaling in fibrosis. Growth Factors 29, 196–202 (2011). [PubMed: 21740331]

149. Eghbali M, Tomek R, Sukhatme VP, Woods C & Bhambi B Differential effects of transforming growth factor-beta 1 and phorbol myristate acetate on cardiac fibroblasts. Regulation of fibrillar collagen mRNAs and expression of early transcription factors. Circ. Res 69, 483–490 (1991). [PubMed: 1860186]

150. Shi Y & Massague J Mechanisms of TGF-beta signaling from cell membrane to the nucleus. Cell 113, 685–700 (2003). [PubMed: 12809600]

151. Feng XH & Derynck R Specificity and versatility in tgf-beta signaling through Smads. Annu. Rev. Cell Dev. Biol 21, 659–693 (2005). [PubMed: 16212511]

152. Chen W & Frangogiannis NG Fibroblasts in post-infarction inflammation and cardiac repair. Biochim. Biophys. Acta 1833, 945–953 (2013). [PubMed: 22982064]

153. Lee AA, Delhaas T, McCulloch AD & Villarreal FJ Differential responses of adult cardiac fibroblasts to in vitro biaxial strain patterns. J. Mol. Cell. Cardiol 31, 1833–1843 (1999). [PubMed: 10525421]

154. Wipff PJ, Rifkin DB, Meister JJ & Hinz B Myofibroblast contraction activates latent TGF-beta1 from the extracellular matrix. J. Cell Biol 179, 1311–1323 (2007). [PubMed: 18086923]

155. van Putten S, Shafieyan Y & Hinz B Mechanical control of cardiac myofibroblasts. J. Mol. Cell. Cardiol 93, 133–142 (2016). [PubMed: 26620422]

156. Jenkins G The role of proteases in transforming growth factor-beta activation. Int. J. Biochem. Cell Biol 40, 1068–1078 (2008). [PubMed: 18243766]

157. Husse B, Briest W, Homagk L, Isenberg G & Gekle M Cyclical mechanical stretch modulates expression of collagen I and collagen III by PKC and tyrosine kinase in cardiac fibroblasts. Am. J. Physiol. Regul. Integr. Comp. Physiol 293, R1898–R1907 (2007). [PubMed: 17686880]

158. Tyagi SC et al. Stretch-induced membrane type matrix metalloproteinase and tissue plasminogen activator in cardiac fibroblast cells. J. Cell. Physiol 176, 374–382 (1998). [PubMed: 9648925]

159. Flynn BP et al. Mechanical strain stabilizes reconstituted collagen fibrils against enzymatic degradation by mammalian collagenase matrix metalloproteinase 8 (MMP-8). PLOS ONE 5, e12337 (2010). [PubMed: 20808784]

160. Chang SW, Flynn BP, Ruberti JW & Buehler MJ Molecular mechanism of force induced stabilization of collagen against enzymatic breakdown. Biomaterials 33, 3852–3859 (2012). [PubMed: 22401852]

161. Yang J et al. Targeting LOXL2 for cardiac interstitial fibrosis and heart failure treatment. Nat. Commun 7, 13710 (2016). [PubMed: 27966531]

162. Gautel M The sarcomeric cytoskeleton: whopicks up the strain? Curr. Opin. Cell Biol 23, 39–46 (2011). [PubMed: 21190822]

163. Spudich JA The myosin swinging cross-bridge model. Nat. Rev. Mol. Cell Biol 2, 387–392 (2001). [PubMed: 11331913]

164. Frank D & Frey N Cardiac Z-disc signaling network. J. Biol. Chem 286, 9897–9904 (2011). [PubMed: 21257757]

165. Granzier HL & Labeit S The giant protein titin: a major player in myocardial mechanics, signaling, and disease. Circ. Res 94, 284–295 (2004). [PubMed: 14976139]

166. Anderson BR & Granzier HL Titin-based tension in the cardiac sarcomere: molecular origin and physiological adaptations. Prog. Biophys. Mol. Biol 110, 204–217 (2012). [PubMed: 22910434]

167. Hoshijima M Mechanical stress-strain sensors embedded in cardiac cytoskeleton: Z disk, titin, and associated structures. Am. J. Physiol. Heart Circ. Physiol 290, H1313–H1325 (2006). [PubMed: 16537787]
168. Arber S, Halder G & Caroni P Muscle LIM protein, a novel essential regulator of myogenesis, promotes myogenic differentiation. Cell 79, 221–231 (1994). [PubMed: 7954791]
169. Heineke J et al. Attenuation of cardiac remodeling after myocardial infarction by muscle LIM protein-calcineurin signaling at the sarcomeric Z-disc. Proc. Natl Acad. Sci. USA 102, 1655–1660 (2005). [PubMed: 15665106]
170. Knoll R et al. The cardiac mechanical stretch sensor machinery involves a Z disc complex that is defective in a subset of human dilated cardiomyopathy. Cell 111, 943–955 (2002). [PubMed: 12507422]
171. Chang DF et al. Cysteine-rich LIM-only proteins CRP1 and CRP2 are potent smooth muscle differentiation cofactors. Dev. Cell 4, 107–118 (2003). [PubMed: 12530967]
172. Linke WA & Kruger M The giant protein titin as an integrator of myocyte signaling pathways. Physiology 25, 186–198 (2010). [PubMed: 20551232]
173. Sheikh F et al. An FHL1-containing complex within the cardiomyocyte sarcomere mediates hypertrophic biomechanical stress responses in mice. J. Clin. Invest 118, 3870–3880 (2008). [PubMed: 19033658]
174. Chu PH, Ruiz-Lozano P, Zhou Q, Cai C & Chen J Expression patterns of FHL/SLIM family members suggest important functional roles in skeletal muscle and cardiovascular system. Mech. Dev 95, 259–265 (2000). [PubMed: 10906474]
175. Gaussin V et al. Common genomic response in different mouse models of beta-adrenergic-induced cardiomyopathy. Circulation 108, 2926–2933 (2003). [PubMed: 14623810]
176. Raskin A et al. A novel mechanism involving four- and-a-half LIM domain protein-1 and extracellular signal-regulated kinase-2 regulates titin phosphorylation and mechanics. J. Biol. Chem 287, 29273–29284 (2012). [PubMed: 22778266]
177. Miller MK et al. The muscle ankyrin repeat proteins: CARP, ankrd2/Arpp and DARP as a family of titin filament-based stress response molecules. J. Mol. Biol 333, 951–964 (2003). [PubMed: 14583192]
178. Barash IA, Mathew L, Ryan AF, Chen J & Lieber RL Rapid muscle-specific gene expression changes after a single bout of eccentric contractions in the mouse. Am. J. Physiol. Cell Physiol 286, C355–C364 (2004). [PubMed: 14561590]
179. Lun AS, Chen J & Lange S Probing muscle ankyrin-repeat protein (MARP) structure and function. Anat. Rec 297, 1615–1629 (2014).
180. Ingber DE, Wang N & Stamenovic D Tensegrity, cellular biophysics, and the mechanics of living systems. Rep. Prog. Phys 77, 046603 (2014). [PubMed: 24695087]
181. Amano M, Nakayama M & Kaibuchi K Rho-kinase/ ROCK: a key regulator of the cytoskeleton and cell polarity. Cytoskeleton 67, 545–554 (2010). [PubMed: 20803696]
182. Mouilleron S, Langer CA, Guettler S, McDonald NQ & Treisman R Structure of a pentavalent G-actin*MRTF-A complex reveals how G-actin controls nucleocytoplasmic shuttling of a transcriptional coactivator. Sci. Signal 4, ra40 (2011). [PubMed: 21673315]
183. Small EM et al. Myocardin-related transcription factor-a controls myofibroblast activation and fibrosis in response to myocardial infarction. Circ. Res 107, 294–304 (2010). [PubMed: 20558820]
184. Codelia VA, Sun G & Irvine KD Regulation of YAP by mechanical strain through Jnk and Hippo signaling. Curr. Biol 24, 2012–2017 (2014). [PubMed: 25127217]
185. Aragona M et al. A mechanical checkpoint controls multicellular growth through YAP/TAZ regulation by actin-processing factors. Cell 154, 1047–1059 (2013). [PubMed: 23954413]
186. Muehlich S, Rehm M, Ebenau A & Goppelt-Struebe M Synergistic induction of CTGF by cytochalasin D and TGFbeta-1 in primary human renal epithelial cells: role of transcriptional regulators MKL1, YAP/TAZ and Smad2/3. Cell. Signal 29, 31–40 (2017). [PubMed: 27721022]
187. Liu F et al. Mechanosignaling through YAP and TAZ drives fibroblast activation and fibrosis. Am. J. Physiol. Lung Cell. Mol. Physiol 308, L344–L357 (2015). [PubMed: 25502501]

188. Chan MW, Hinz B & McCulloch CA Mechanical induction of gene expression in connective tissue cells. Methods Cell Biol 98, 178–205 (2010). [PubMed: 20816235]

189. Fedorchak GR, Kaminski A & Lammerding J Cellular mechanosensing: getting to the nucleus of it all. Prog. Biophys. Mol. Biol 115, 76–92 (2014). [PubMed: 25008017]

190. Crisp M et al. Coupling of the nucleus and cytoplasm: role of the LINC complex. J. Cell Biol 172, 41–53 (2006). [PubMed: 16380439]

191. Lammerding J, Kamm RD & Lee RT Mechanotransduction in cardiac myocytes. Ann. NY Acad. Sci 1015, 53–70 (2004). [PubMed: 15201149]

192. Enyedi B & Niethammer P Nuclear membrane stretch and its role in mechanotransduction. Nucleus 8, 156–161 (2017). [PubMed: 28112995]

193. Caputo S et al. The carboxyl-terminal nucleoplasmic region of MAN1 exhibits a DNA binding winged helix domain. J. Biol. Chem 281, 18208–18215 (2006). [PubMed: 16648637]

194. Chang W, Worman HJ & Gundersen GG Accessorizing and anchoring the LINC complex for multifunctionality. J. Cell Biol 208, 11–22 (2015). [PubMed: 25559183]

195. Guilluy C et al. Isolated nuclei adapt to force and reveal a mechanotransduction pathway in the nucleus. Nat. Cell Biol 16, 376–381 (2014). [PubMed: 24609268]

196. Cupesi M et al. Attenuated hypertrophic response to pressure overload in a lamin A/C haploinsufficiency mouse. J. Mol. Cell. Cardiol 48, 1290–1297 (2010). [PubMed: 19913544]

197. Enyedi B, Jelcic M & Niethammer P The cell nucleus serves as a mechanotransducer of tissue damage-induced inflammation. Cell 165, 1160–1170 (2016). [PubMed: 27203112]

198. Schreiber KH & Kennedy BK When lamins go bad: nuclear structure and disease. Cell 152, 1365–1375 (2013). [PubMed: 23498943]

199. Komaki H et al. Inflammatory changes in infantile-onset LMNA-associated myopathy. Neuromuscul. Disord 21, 563–568 (2011). [PubMed: 21632249]

200. Iyer KV, Pulford S, Mogilner A & Shivashankar GV Mechanical activation of cells induces chromatin remodeling preceding MKL nuclear transport. Biophys. J 103, 1416–1428 (2012). [PubMed: 23062334]

201. Furusawa T et al. Chromatin decompaction by the nucleosomal binding protein HMGN5 impairs nuclear sturdiness. Nat. Commun 6, 6138 (2015). [PubMed: 25609380]

202. Rochman M et al. The interaction of NSBP1/HMGN5 with nucleosomes in euchromatin counteracts linker histone-mediated chromatin compaction and modulates transcription. Mol. Cell 35, 642–656 (2009). [PubMed: 19748358]

203. Nikolova V et al. Defects in nuclear structure and function promote dilated cardiomyopathy in lamin A/C-deficient mice. J. Clin. Invest 113, 357–369 (2004). [PubMed: 14755333]

204. Ho CY, Jaalouk DE, Vartiainen MK & Lammerding J Lamin A/C and emerin regulate MKL1-SRF activity by modulating actin dynamics. Nature 497, 507–511 (2013). [PubMed: 23644458]

205. Thomas CH, Collier JH, Sfeir CS & Healy KE Engineering gene expression and protein synthesis by modulation of nuclear shape. Proc. Natl Acad. Sci. USA 99, 1972–1977 (2002). [PubMed: 11842191]

206. Alam SG et al. The mammalian LINC complex regulates genome transcriptional responses to substrate rigidity. Sci. Rep 6, 38063 (2016). [PubMed: 27905489]

207. Lovett DB, Shekhar N, Nickerson JA, Roux KJ & Lele TP Modulation of nuclear shape by substrate rigidity. Cell. Mol. Bioeng 6, 230–238 (2013). [PubMed: 23914256]

208. Vermij SH, Abriel H & van Veen TA Refining the molecular organization of the cardiac intercalated disc. Cardiovasc. Res 113, 259–275 (2017). [PubMed: 28069669]

209. Sheikh F, Ross RS & Chen J Cell-cell connection to cardiac disease. Trends Cardiovasc. Med 19, 182–190 (2009). [PubMed: 20211433]

210. Yoshida M et al. Weaving hypothesis of cardiomyocyte sarcomeres: discovery of periodic broadening and narrowing of intercalated disk during volume-load change. Am. J. Pathol 176, 660–678 (2010). [PubMed: 20056839]

211. Mezzano V & Sheikh F Cell-cell junction remodeling in the heart: possible role in cardiac conduction system function and arrhythmias? Life Sci 90, 313–321 (2012). [PubMed: 22227473]

212. Michaelson JE & Huang H Cell-cell junctional proteins in cardiovascular mechanotransduction. Ann. Biomed. Engineer 40, 568–577 (2012).

213. Chopra A, Tabdanov E, Patel H, Janmey PA & Kresh JY Cardiac myocyte remodeling mediated by N-cadherin-dependent mechanosensing. Am. J. Physiol. Heart Circ. Physiol 300, H1252–H1266 (2011). [PubMed: 21257918]

214. Kostetskii I et al. Induced deletion of the N-cadherin gene in the heart leads to dissolution of the intercalated disc structure. Circ. Res 96, 346–354 (2005). [PubMed: 15662031]

215. Yonemura S, Wada Y, Watanabe T, Nagafuchi A & Shibata M alpha-Catenin as a tension transducer that induces adherens junction development. Nat. Cell Biol 12, 533–542 (2010). [PubMed: 20453849]

216. Vite A, Zhang C, Yi R, Emms S & Radice GL alpha-Catenin-dependent cytoskeletal tension controls Yap activity in the heart. Development 145, dev149823 (2018).

217. Sheikh F et al. alpha-E-catenin inactivation disrupts the cardiomyocyte adherens junction, resulting in cardiomyopathy and susceptibility to wall rupture. Circulation 114, 1046–1055 (2006). [PubMed: 16923756]

218. Ehler E et al. Alterations at the intercalated disk associated with the absence of muscle LIM protein. J. Cell Biol 153, 763–772 (2001). [PubMed: 11352937]

219. Zhang JQ et al. Ultrastructural and biochemical localization of N-RAP at the interface between myofibrils and intercalated disks in the mouse heart. Biochemistry 40, 14898–14906 (2001). [PubMed: 11732910]

220. Hariharan V et al. Arrhythmogenic right ventricular cardiomyopathy mutations alter shear response without changes in cell-cell adhesion. Cardiovasc. Res 104, 280–289 (2014). [PubMed: 25253076]

221. Yang Z et al. Desmosomal dysfunction due to mutations in desmoplakin causes arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circ. Res 99, 646–655 (2006). [PubMed: 16917092]

222. Lyon RC et al. Connexin defects underlie arrhythmogenic right ventricular cardiomyopathy in a novel mouse model. Hum. Mol. Genet 23, 1134–1150 (2014). [PubMed: 24108106]

223. Pilichou K et al. Mutations in desmoglein-2 gene are associated with arrhythmogenic right ventricular cardiomyopathy. Circulation 113, 1171–1179 (2006). [PubMed: 16505173]

224. Salameh A et al. Opposing and synergistic effects of cyclic mechanical stretch and alpha- or beta-adrenergic stimulation on the cardiac gap junction protein Cx43. Pharmacol. Res 62, 506–513 (2010). [PubMed: 20705136]

225. Zhuang J, Yamada KA, Saffitz JE & Kleber AG Pulsatile stretch remodels cell-to-cell communication in cultured myocytes. Circ. Res 87, 316–322 (2000). [PubMed: 10948066]

226. Wang Q et al. Xin proteins and intercalated disc maturation, signaling and diseases. Front. Biosci 17, 2566–2593 (2012).

227. Chilton L et al. K+ currents regulate the resting membrane potential, proliferation, and contractile responses in ventricular fibroblasts and myofibroblasts. Am. J. Physiol. Heart Circ. Physiol 288, H2931–H2939 (2005). [PubMed: 15653752]

228. Miragoli M, Gaudesius G & Rohr S Electrotonic modulation of cardiac impulse conduction by myofibroblasts. Circ. Res 98, 801–810 (2006). [PubMed: 16484613]

229. Rohr S Myofibroblasts in diseased hearts: new players in cardiac arrhythmias? Heart Rhythm 6, 848–856 (2009). [PubMed: 19467515]

230. Kohl P, Camelliti P, Burton FL & Smith GL Electrical coupling of fibroblasts and myocytes: relevance for cardiac propagation. J. Electrocardiol 38, 45–50 (2005). [PubMed: 16226073]

231. Zlochiver S et al. Electrotonic myofibroblast-to-myocyte coupling increases propensity to reentrant arrhythmias in two-dimensional cardiac monolayers. Biophys. J 95, 4469–4480 (2008). [PubMed: 18658226]

232. Rohr S Arrhythmogenic implications of fibroblast-myocyte interactions. Circ. Arrhythm. Electrophysiol 5, 442–452 (2012). [PubMed: 22511661]

233. Quinn TA et al. Electrotonic coupling of excitable and nonexcitable cells in the heart revealed by optogenetics. Proc. Natl Acad. Sci. USA 113, 14852–14857 (2016). [PubMed: 27930302]

234. Ongstad E & Kohl P Fibroblast-myocyte coupling in the heart: potential relevance for therapeutic interventions. J. Mol. Cell. Cardiol 91, 238–246 (2016). [PubMed: 26774702]

235. Roell W et al. Overexpression of Cx43 in cells of the myocardial scar: correction of post-infarct arrhythmias through heterotypic cell-cell coupling. Sci. Rep 8, 7145 (2018). [PubMed: 29739982]

236. Shyu KG, Ko WH, Yang WS, Wang BW & Kuan P Insulin-like growth factor-1 mediates stretch-induced upregulation of myostatin expression in neonatal rat cardiomyocytes. Cardiovasc. Res 68, 405–414 (2005). [PubMed: 16125157]

237. Pemberton CJ, Raudsepp SD, Yandle TG, Cameron VA & Richards AM Plasma cardiotrophin-1 is elevated in human hypertension and stimulated by ventricular stretch. Cardiovasc. Res 68, 109–117 (2005). [PubMed: 15978561]

238. Bowers SLK, Borg TK & Baudino TA The dynamics of fibroblast–myocyte–capillary interactions in the heart. Ann. NY Acad. Sci 1188, 143–152 (2010). [PubMed: 20201897]

239. Weinberg EO et al. Sex dependence and temporal dependence of the left ventricular genomic response to pressure overload. Physiol. Genom 12, 113–127 (2003).

240. Wang D et al. Effects of pressure overload on extracellular matrix expression in the heart of the atrial natriuretic peptide-null mouse. Hypertension 42, 88–95 (2003). [PubMed: 12756220]

241. Miyazaki H et al. Comparison of gene expression profiling in pressure and volume overload-induced myocardial hypertrophies in rats. Hypertens. Res 29, 1029–1045 (2006). [PubMed: 17378376]

242. Zheng J et al. Microarray identifies extensive downregulation of noncollagen extracellular matrix and profibrotic growth factor genes in chronic isolated mitral regurgitation in the dog. Circulation 119, 2086–2095 (2009). [PubMed: 19349319]

243. Blaxall BC, Tschannen-Moran BM, Milano CA & Koch WJ Differential gene expression and genomic patient stratification following left ventricular assist device support. J. Am. Coll. Cardiol 41, 1096–1106 (2003). [PubMed: 12679207]

244. Birks EJ et al. Gene profiling changes in cytoskeletal proteins during clinical recovery after left ventricular-assist device support. Circulation 112, I57–64 (2005). [PubMed: 16159866]

245. Margulies KB et al. Mixed messages: transcription patterns in failing and recovering human myocardium. Circ. Res 96, 592–599 (2005). [PubMed: 15718504]

246. Matkovich SJ et al. Reciprocal regulation of myocardial microRNAs and messenger RNA in human cardiomyopathy and reversal of the microRNA signature by biomechanical support. Circulation 119, 1263–1271 (2009). [PubMed: 19237659]

247. Yang KC et al. Deep RNA sequencing reveals dynamic regulation of myocardial noncoding RNAs in failing human heart and remodeling with mechanical circulatory support. Circulation 129, 1009–1021 (2014). [PubMed: 24429688]

248. Terracciano CM et al. Clinical recovery from end-stage heart failure using left-ventricular assist device and pharmacological therapy correlates with increased sarcoplasmic reticulum calcium content but not with regression of cellular hypertrophy. Circulation 109, 2263–2265 (2004). [PubMed: 15136495]

249. Weinberg EO et al. Expression and regulation of ST2, an interleukin-1 receptor family member, in cardiomyocytes and myocardial infarction. Circulation 106, 2961–2966 (2002). [PubMed: 12460879]

250. Kakkar R & Lee RT The IL-33/ST2 pathway: therapeutic target and novel biomarker. Nat. Rev. Drug Discov 7, 827–840 (2008). [PubMed: 18827826]

251. de Boer RA, Daniels LB, Maisel AS & Januzzi JL Jr. State of the Art: Newer biomarkers in heart failure. Eur. J. Heart Fail 17, 559–569 (2015). [PubMed: 25880523]

252. Frank D et al. Gene expression pattern in biomechanically stretched cardiomyocytes: evidence for a stretch-specific gene program. Hypertension 51, 309–318 (2008). [PubMed: 18158353]

253. McCain ML, Sheehy SP, Grosberg A, Goss JA & Parker KK Recapitulating maladaptive, multiscale remodeling of failing myocardium on a chip. Proc. Natl Acad. Sci. USA 110, 9770–9775 (2013). [PubMed: 23716679]

254. Rysa J, Tokola H & Ruskoaho H Mechanical stretch induced transcriptomic profiles in cardiac myocytes. Sci. Rep 8, 4733 (2018). [PubMed: 29549296]

255. Kessler D et al. Fibroblasts in mechanically stressed collagen lattices assume a “synthetic” phenotype. J. Biol. Chem 276, 36575–36585 (2001). [PubMed: 11468280]

256. Driesen RB et al. Reversible and irreversible differentiation of cardiac fibroblasts. Cardiovasc. Res 101, 411–422 (2014). [PubMed: 24368833]

257. Haggart CR, Ames EG, Lee JK & Holmes JW Effects of stretch and shortening on gene expression in intact myocardium. Physiol. Genomics 46, 57–65 (2014). [PubMed: 24302644]

258. Hirt MN et al. Increased afterload induces pathological cardiac hypertrophy: a new in vitro model. Bas. Res. Cardiol 107, 307 (2012).

259. Boon RA & Dimmeler S MicroRNAs in myocardial infarction. Nat. Rev. Cardiol 12, 135–142 (2015). [PubMed: 25511085]

260. van Rooij E et al. A signature pattern of stress-responsive microRNAs that can evoke cardiac hypertrophy and heart failure. Proc. Natl Acad. Sci. USA 103, 18255–18260 (2006). [PubMed: 17108080]

261. Frank D et al. MicroRNA-20a inhibits stress-induced cardiomyocyte apoptosis involving its novel target Egln3/PHD3. J. Mol. Cell. Cardiol 52, 711–717 (2012). [PubMed: 22182733]

262. van Rooij E et al. Control of stress-dependent cardiac growth and gene expression by a microRNA. Science 316, 575–579 (2007). [PubMed: 17379774]

263. Callis TE et al. MicroRNA-208a is a regulator of cardiac hypertrophy and conduction in mice. J. Clin. Invest 119, 2772–2786 (2009). [PubMed: 19726871]

264. Shyu KG, Wang BW, Wu GJ, Lin CM & Chang H Mechanical stretch via transforming growth factor-beta1 activates microRNA208a to regulate endoglin expression in cultured rat cardiac myoblasts. Eur. J. Heart Fail 15, 36–45 (2013). [PubMed: 22941949]

265. Wang BW, Wu GJ, Cheng WP & Shyu KG Mechanical stretch via transforming growth factor-beta1 activates microRNA-208a to regulate hypertrophy in cultured rat cardiac myocytes. J. Formos. Med. Assoc 112, 635–643 (2013). [PubMed: 24120154]

266. Ransohoff JD, Wei Y & Khavari PA The functions and unique features of long intergenic non-coding RNA. Nat. Rev. Mol. Cell Biol 19, 143–157 (2018). [PubMed: 29138516]

267. Sallam T, Sandhu J & Tontonoz P Long noncoding RNA discovery in cardiovascular disease: decoding form to function. Circ. Res 122, 155–166 (2018). [PubMed: 29301847]

268. Carrion K et al. The long non-coding HOTAIR is modulated by cyclic stretch and WNT/beta-CATENIN in human aortic valve cells and is a novel repressor of calcification genes. PLOS ONE 9, e96577 (2014). [PubMed: 24788418]

269. Yang JH & Saucerman JJ Computational models reduce complexity and accelerate insight into cardiac signaling networks. Circ. Res 108, 85–97 (2011). [PubMed: 21212391]

270. Noble D Modeling the heart—from genes to cells to the whole organ. Science 295, 1678–1682 (2002). [PubMed: 11872832]

271. Huxley AF Muscle structure and theories of contraction. Prog. Biophys. Biophys. Chem 7, 255–318 (1957). [PubMed: 13485191]

272. Noble D Cardiac action and pacemaker potentials based on the Hodgkin-Huxley equations. Nature 188, 495–497 (1960).

273. Jafri MS, Rice JJ & Winslow RL Cardiac Ca^{2+} dynamics: the roles of ryanodine receptor adaptation and sarcoplasmic reticulum load. Biophys. J 74, 1149–1168 (1998). [PubMed: 9512016]

274. Luo CH & Rudy Y A dynamic model of the cardiac ventricular action potential. Afterdepolarizations, II. triggered activity, and potentiation. Circ. Res 74, 1097–1113 (1994). [PubMed: 7514510]

275. Cortassa S, Aon MA, Marban E, Winslow RL & O’Rourke B An integrated model of cardiac mitochondrial energy metabolism and calcium dynamics. Biophys. J 84, 2734–2755 (2003). [PubMed: 12668482]

276. Beard DA A biophysical model of the mitochondrial respiratory system and oxidative phosphorylation. PLOS Comput. Biol 1, e36 (2005). [PubMed: 16163394]

277. Saucerman JJ, Brunton LL, Michailova AP & McCulloch AD Modeling beta-adrenergic control of cardiac myocyte contractility in silico. J. Biol. Chem 278, 47997–48003 (2003). [PubMed: 12972422]

278. Hund TJ & Rudy Y Rate dependence and regulation of action potential and calcium transient in a canine cardiac ventricular cell model. Circulation 110, 3168–3174 (2004). [PubMed: 15505083]

279. Winslow RL, Rice J, Jafri S, Marban E & O'Rourke B Mechanisms of altered excitation-contraction coupling in canine tachycardia-induced heart failure, II: model studies. Circ. Res 84, 571–586 (1999). [PubMed: 10082479]

280. Kang JH, Lee HS, Kang YW & Cho KH Systems biological approaches to the cardiac signaling network. Brief Bioinform 17, 419–428 (2016). [PubMed: 26108228]

281. Tavi P et al. Pacing-induced calcineurin activation controls cardiac Ca^{2+} signalling and gene expression. J. Physiol 554, 309–320 (2004). [PubMed: 14565991]

282. Berridge MJ, Bootman MD & Roderick HL Calcium signalling: dynamics, homeostasis and remodelling. Nat. Rev. Mol. Cell Biol 4, 517–529 (2003). [PubMed: 12838335]

283. Colella M et al. Ca^{2+} oscillation frequency decoding in cardiac cell hypertrophy: role of calcineurin/NFAT as Ca^{2+} signal integrators. Proc. Natl Acad. Sci. USA 105, 2859–2864 (2008). [PubMed: 18287024]

284. Saucerman JJ & Bers DM Calmodulin mediates differential sensitivity of CaMKII and calcineurin to local Ca^{2+} in cardiac myocytes. Biophys. J 95, 4597–4612 (2008). [PubMed: 18689454]

285. Cooling MT, Hunter P & Crampin EJ Sensitivity of NFAT cycling to cytosolic calcium concentration: implications for hypertrophic signals in cardiac myocytes. Biophys. J 96, 2095–2104 (2009). [PubMed: 19289036]

286. Cooling M, Hunter P & Crampin EJ Modeling hypertrophic IP3 transients in the cardiac myocyte. Biophys. J 93, 3421–3433 (2007). [PubMed: 17693463]

287. Shin SY, Yang HW, Kim JR, Heo WD & Cho KH A hidden incoherent switch regulates RCAN1 in the calcineurin-NFAT signaling network. J. Cell Sci 124, 82–90 (2011). [PubMed: 21172821]

288. Ryall KA et al. Network reconstruction and systems analysis of cardiac myocyte hypertrophy signaling. J. Biol. Chem 287, 42259–42268 (2012). [PubMed: 23091058]

289. Molkentin JD & Robbins J With great power comes great responsibility: using mouse genetics to study cardiac hypertrophy and failure. J. Mol. Cell. Cardiol 46, 130–136 (2009). [PubMed: 18845155]

290. Cook SA, Clerk A & Sugden PH Are transgenic mice the 'alkahest' to understanding myocardial hypertrophy and failure? J. Mol. Cell. Cardiol 46, 118–129 (2009). [PubMed: 19071133]

291. Frank DU, Sutcliffe MD & Saucerman JJ Network-based predictions of in vivo cardiac hypertrophy. J. Mol. Cell. Cardiol 121, 180–189 (2018). [PubMed: 30030017]

292. Cheng B et al. Cellular mechanosensing of the biophysical microenvironment: A review of mathematical models of biophysical regulation of cell responses. Phys. Life Rev 22–23, 88–119 (2017).

293. Novak IL, Slepchenko BM, Mogilner A & Loew LM Cooperativity between cell contractility and adhesion. Phys. Rev. Lett 93, 268109 (2004). [PubMed: 15698031]

294. Deshpande VS, McMeeking RM & Evans AG A bio-chemo-mechanical model for cell contractility. Proc. Natl Acad. Sci. USA 103, 14015–14020 (2006). [PubMed: 16959880]

295. Chen K et al. Role of boundary conditions in determining cell alignment in response to stretch. Proc. Natl Acad. Sci. USA 115, 986–991 (2018). [PubMed: 29343646]

296. Grosberg A et al. Self-organization of muscle cell structure and function. PLOS Comput. Biol 7, e1001088 (2011). [PubMed: 21390276]

297. Livne A & Geiger B The inner workings of stress fibers - from contractile machinery to focal adhesions and back. J. Cell Sci 129, 1293–1304 (2016). [PubMed: 27037413]

298. Yuan H, Marzban B & Kit Parker K Myofibrils in cardiomyocytes tend to assemble along the maximal principle stress directions. J. Biomech. Eng 139, 121010 (2017).

299. McCain ML, Lee H, Aratyn-Schaus Y, Kleber AG & Parker KK Cooperative coupling of cell-matrix and cell-cell adhesions in cardiac muscle. Proc. Natl Acad. Sci. USA 109, 9881–9886 (2012). [PubMed: 22675119]
300. Lee LC, Kassab GS & Guccione JM Mathematical modeling of cardiac growth and remodeling. Wiley Interdiscip. Rev. Syst. Biol. Med 8, 211–226 (2016). [PubMed: 26952285]
301. Dingal PC & Discher DE Systems mechanobiology: tension-inhibited protein turnover is sufficient to physically control gene circuits. Biophys. J 107, 2734–2743 (2014). [PubMed: 25468352]
302. Sharp WW, Terracio L, Borg TK & Samarel AM Contractile activity modulates actin synthesis and turnover in cultured neonatal rat heart cells. Circ. Res 73, 172–183 (1993). [PubMed: 8508528]
303. Schroer AK, Ryzhova LM & Merryman WD Network modeling approach to predict myofibroblast differentiation. Cell. Mol. Bioengineer 7, 446–459 (2014).
304. Dupont S et al. Role of YAP/TAZ in mechanotransduction. Nature 474, 179–183 (2011). [PubMed: 21654799]
305. Sun M, Spill F & Zaman MHA Computational model of YAP/TAZ mechanosensing. Biophys. J 110, 2540–2550 (2016). [PubMed: 27276271]
306. Yang X et al. LATS1 tumour suppressor affects cytokinesis by inhibiting LIMK1. Nat. Cell Biol 6, 609–617 (2004). [PubMed: 15220930]
307. Zeigler AC, Richardson WJ, Holmes JW & Saucerman JJ A computational model of cardiac fibroblast signaling predicts context-dependent drivers of myofibroblast differentiation. J. Mol. Cell. Cardiol 94, 72–81 (2016). [PubMed: 27017945]
308. Khalil H et al. Fibroblast-specific TGF-beta-Smad2/3 signaling underlies cardiac fibrosis. J. Clin. Invest 127, 3770–3783 (2017). [PubMed: 28891814]
309. Tan PM, Buchholz KS, Omens JH, McCulloch AD & Saucerman JJ Predictive model identifies key network regulators of cardiomyocyte mechano-signaling. PLOS Comput. Biol 13, e1005854 (2017). [PubMed: 29131824]
310. Lu HI et al. Entresto therapy effectively protects heart and lung against transverse aortic constriction induced cardiopulmonary syndrome injury in rat. Am. J. Transl Res 10, 2290–2305 (2018). [PubMed: 30210671]
311. von Lueder TG et al. Angiotensin receptor neprilysin inhibitor LCZ696 attenuates cardiac remodeling and dysfunction after myocardial infarction by reducing cardiac fibrosis and hypertrophy. Circ. Heart Fail 8, 71–78 (2015). [PubMed: 25362207]
312. Suematsu Y et al. LCZ696 (Sacubitril/Valsartan), an angiotensin-receptor neprilysin inhibitor, attenuates cardiac hypertrophy, fibrosis, and vasculopathy in a rat model of chronic kidney disease. J. Card. Fail 24, 266–275 (2018). [PubMed: 29325796]
313. Ambrosi D et al. Perspectives on biological growth and remodeling. J. Mech. Phys. Solids 59, 863–883 (2011). [PubMed: 21532929]
314. Witzenburg CM & Holmes JWA Comparison of phenomenologic growth laws for myocardial hypertrophy. J. Elast 129, 257–281 (2017). [PubMed: 29632418]
315. Kerckhoffs RC, Omens J & McCulloch AD A single strain-based growth law predicts concentric and eccentric cardiac growth during pressure and volume overload. Mech. Res. Commun 42, 40–50 (2012). [PubMed: 22639476]
316. Young AA, Orr R, Smaill BH & Dell'Italia LJ Three-dimensional changes in left and right ventricular geometry in chronic mitral regurgitation. Am. J. Physiol 271, H2689–H2700 (1996). [PubMed: 8997332]
317. Nagatomo Y et al. Translational mechanisms accelerate the rate of protein synthesis during canine pressure-overload hypertrophy. Am. J. Physiol 277, H2176–H2184 (1999). [PubMed: 10600835]
318. Rouillard AD & Holmes JW Coupled agent-based and finite-element models for predicting scar structure following myocardial infarction. Prog. Biophys. Mol. Biol 115, 235–243 (2014). [PubMed: 25009995]
319. Yamamoto K et al. Regulation of cardiomyocyte mechanotransduction by the cardiac cycle. Circulation 103, 1459–1464 (2001). [PubMed: 11245653]

320. Russell B, Curtis MW, Koshman YE & Samarel AM Mechanical stress-induced sarcomere assembly for cardiac muscle growth in length and width. J. Mol. Cell. Cardiol 48, 817–823 (2010). [PubMed: 20188736]

321. DrugMonkey. Generalization, not “reproducibility” Scientopia http://drugmonkey.scientopia.org/2018/02/26/generalization-not-reproducibility/ (2018).

322. Boerma M et al. Microarray analysis of gene expression profiles of cardiac myocytes and fibroblasts after mechanical stress, ionising or ultraviolet radiation. BMC Genomics 6, 6 (2005). [PubMed: 15656902]

Key points

- The complex remodelling processes in the myocardium are regulated by mechanical signals that are sensed and transduced into transcriptional responses by cardiac myocytes and fibroblasts.
- Mechanosensitive pathways regulate expression of genes that encode proteins mediating cardiac myocyte hypertrophy, myofibroblast differentiation and remodelling of the extracellular matrix.
- Mathematical systems models are beginning to address outstanding challenges regarding how cardiac cells integrate complex mechanical and biochemical signals to coordinate gene expression and cell remodelling.
- Integrative experimental and computational mechanotransduction studies should provide further insights into mechanisms and potential therapies for mechano-based diseases, including chronic tissue and chamber pathological remodelling.

Box 1 |

Challenges in understanding complex mechanoregulation of cardiac cells

What are the specific mechanical signals that are transduced by particular mechanosensitive proteins?

Some studies have shown distinct remodelling or transcriptional responses of cardiac myocytes to the timing[319] or direction of stretch[253,320] and to externally applied versus cell-generated stresses or strains[257]. These factors cannot be independently controlled in most experimental systems; therefore, studies on particular mechanosensitive proteins have largely used a single mechanical stimulus.

Are downstream mechanosensitive pathways and gene expression sensitive to signals propagating from specific mechanosensors?

The majority of studies examining mechanoresponsive changes in global gene expression have not directly perturbed putative mechanosensors[206]. Such experiments are complicated because putative mechanosensor proteins have pleiotropic signalling or structural roles that cannot easily be dissociated from mechanosensing mechanisms.

How do downstream mechanosensitive pathways integrate combined inputs from multiple mechanosensors and biochemical stimuli?

Cardiac stresses are multifactorial. Many mechanosensors are likely to respond to a given mechanical stimulus, but combinatorial perturbations to mechanosensors have rarely been performed. Feedback between mechanosensory pathways (such as mutually reinforcing focal adhesions and stress fibres) and with autocrine or paracrine factors (such as angiotensin II, endothelin 1 or transforming growth factor-β) complicates interpretation.

To what extent does mechanosignalling generalize across experimental contexts?

As in other areas of science[321], integration of data between laboratories and experimental systems is challenged by the unknown extent to which mechanosignalling mechanisms and responses depend on experimental variables, such as genetic background, surgical technique or cell culture conditions.

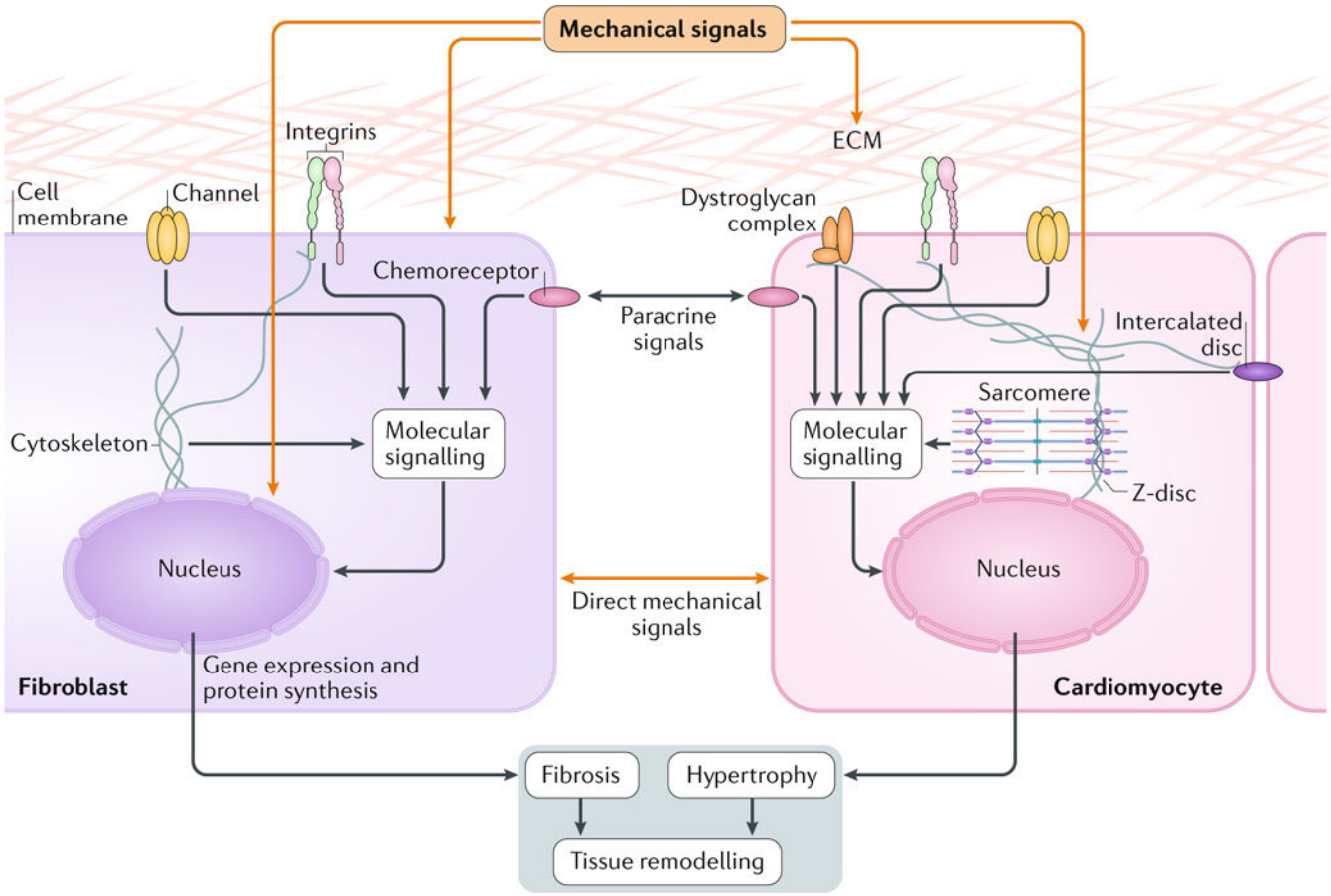

Fig. 1. Major mechanosensitive mechanisms and pathways in cardiac fibroblasts and myocytes.

Mechanical signals that act on the extracellular matrix (ECM) and cell membranes and internally on the cytoskeleton and nucleus initiate complex molecular signalling cascades, leading to changes in gene expression and protein synthesis in both cell types. Direct and indirect interactions between cells also mediate these responses. The net result of the changes in the mechanical cues is tissue remodelling and, in many cases, pathophysiological outcomes.

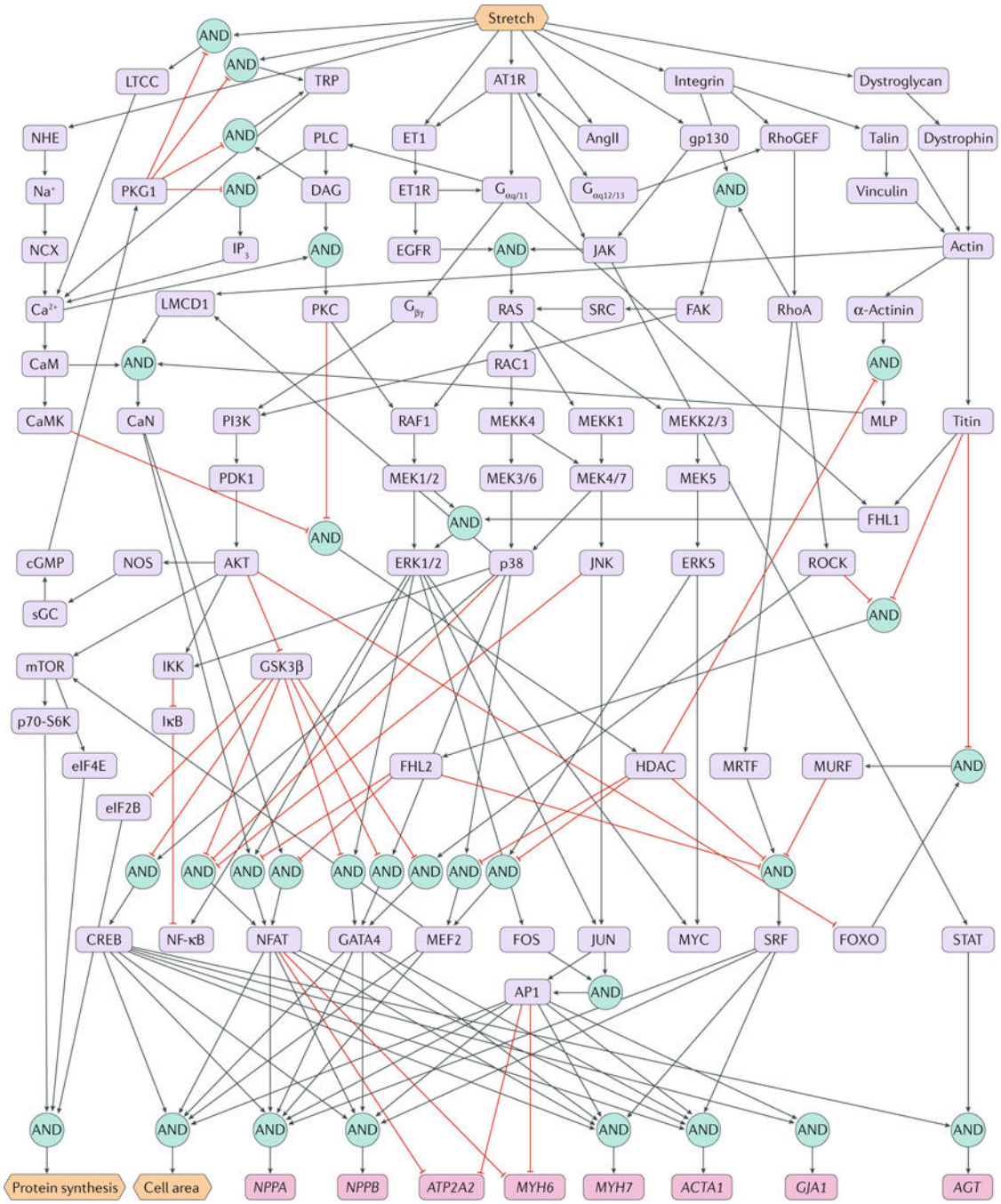

Fig. 2. Systems model of the cardiac myocyte signalling network.

The model predicts how mechanical stretch is sensed by nine proteins to regulate transcription factors, protein synthesis, cell size and gene expression of *NPPA* (encoding atrial natriuretic peptide), *NPPB* (encoding B-type natriuretic peptide), *ATP2A2* (encoding sarcoplasmic/endoplasmic reticulum calcium ATPase), *MYH6* (encoding α-myosin heavy chain), MYH7 (encoding β-myosin heavy chain), *ACTA1* (encoding skeletal α-actin), *GJA1* (encoding connexin 43) and *AGT* (encoding angiotensinogen). AND logic gates indicate multiplicative activation or inhibition of the downstream node. Adapted from REF.[309], CC-

BY-4.0 (https://creativecommons.org/licenses/by/4.0/), and details of the model logic can be found in this publication.

Table 1 |

Mechanoresponsive gene programmes in the heart and specific cardiac cells

Experimental system	Gene sets	Example genes	Refs
Cardiac pressure overload	NP, ECM and metabolismi	*CTGF* and *FHL1*	239
	NP and ECM	*POSTN* and *SPP1*	240
	NP and ECM	*LOXL1, MT1* and *PDK1*	241
Cardiac volume overload	NP, ECM and cytoskeleton	*MT1* and *TAGLN*	241
	Decreased ECM	*MMP1, MMP9* and decreased *CTGF*	242
Patients after LVAD implantation	NP, ECM and metabolismi	*HSPB6* and *MT1*	243
	Sarcomere, cytoskeleton, ECM and FA	*ITGB1* and *VCL*	244
	Limited	*PDK1* and SOCS3	245
	Limited	*CRYM, TNNT3* and multiple microRNAs	246
	Limited	Multiple lncRNAs	247
Engineered heart tissue	NP, ECM, sarcomere and metabolism	*ACTA1* and *COL1A1*	258
Papillary muscle	NP, ECM and sarcomere	*CTGF* and *HSP90AB1*	257
Cardiac myocytes	Not reported	*IL1RL1*	249
	NP, sarcomere and cell adhesion	*FHL1, GDF15* and *HMOX1*	252
	ECM, FA and sarcomere	*TRPC1* and *ITGA6*	253
	ECM, cytoskeleton and metabolism	–	322
	NP and proliferation	*SERPINB2* and let-7 family	254
Fibroblasts	ECM, FA, cytoskeleton and proliferation	*CTGF* and *SERPINB2*	255
	FA, proliferation and TGFβ signalling	–	256
	ECM, FA, cytoskeleton and proliferation	–	206

Gene expression measured by cDNA microarrays or RNA sequencing. ECM, extracellular matrix; FA, focal adhesions; lncRNA, long non-coding RNA; LVAD, left ventricular assist device; NP, natriuretic peptides; TGFβ, transforming growth factor-β.