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The effect of mechanical strain on soft (cardiovascular) and hard (bone) tissues

Common pathways for different biological outcomes

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Mechanical stress plays a pivotal role in developing and maintaining tissues functionalities. Cells are constantly subjected to strain and compressive forces that are sensed by specialized membrane mechanosensors and converted in biochemical signals able to differently influence cellular behavior in terms of surviving, differentiation and extracellular matrix remodeling. This review focuses on the effects of mechanical strain on soft and hard tissues.

Unexpectedly, different cells share almost the same membrane mechanosensors and the relative intracellular pathways, but to ultimately obtain very different biological effects. The events occurring in cardiovascular and bone tissues are treated in details, showing that integrins, cadherins, growth factor receptors and ions channels specifically expressed in the different tissues are the major actors of the sight. However, MAPkinases and RhoGTPases are mainly involved in the biochemical intracellular signaling directed to nuclear modifications.

Bone and Mechanical Stress: Role of Strain on Cell Behavior

Bone is a very complex tissue useful for a variety of functions. In fact, skeleton offers structural support for the rest of the body, permits movement and locomotion by providing levers for the muscles, protects internal organs and structures, provides maintenance of mineral homeostasis and acid-base balance, serves as a reservoir of growth factors and cytokines and provides the environment for hematopoiesis within the marrow spaces. Each bone is constantly subjected to modeling during life to adapt its architecture and function to biomechanical forces, as well as remodeling to replace old and damaged bone with new to maintain bone strength.[1] Moreover, bone remodeling provides Ca^{2+} in case of need, as the mineralized extracellular matrix furnishes as reservoir, and this process is finely modulated by the endocrine system.[2] The adaption of bone to mechanical stress is controlled at the cellular level through the coordinated actions of osteoblasts, osteocytes and osteoclasts and these loading forces lead to an increase in bone mass through a positive shift in the balance between bone formation and bone resorption. It is known that bone is formed in areas where loads are elevated and bone is necessary, and resorbed where strains and stresses are absent and bone is excessive.[3-5]

Many experimental data in vitro and in vivo indicate the osteocytes as the main sensor detecting mechanical forces in the bone tissue.[6-9] Osteocytes comprise 90–95% of all bone cells in the adult skeleton, and they are located in the mineralized bone matrix within lacunae. Indeed, they have many cytoplasmic processes that stretch out within bone matrix channels called canaliculi. Through their complex communication network, osteocytes are able to mediate the effects of bone loading and respond by sending signals to the bone-forming osteoblasts and the bone-absorbing osteoclasts, thereby guiding the bone remodeling process (**Fig. 1**).

The other candidates for the role of the mechanosensory cell in bone tissue are the osteoblasts, the bone lining cells and the osteoclasts, but because of their number, lifetime and function, the only other real candidate is represented by the osteoblast. However, because of their surface location they must have a great sensitivity to sense a small strain characteristic of the bone. The application of force to the skeletal system produces several potential stimuli for osteocyte function, including hydrostatic pressure, fluid-flow-induced shear stress and bone tissue strain.[7] The response of bone to mechanical solicitations will depend on magnitude, strain rate, strain distribution, number of loading cycles and frequency.

It has been shown that fluid flow and direct mechanical stimulation have different effects on bone cells. In this review we focused our attention on mechanical strain that is represented by the geometric deformation within the material and is expressed as the ratio between the length change and original length. Different kinds of strain are present in the bone, but we only considered the axial strain. By definition, axial strain comprises both compressive and tensile strain in the same direction as the applied load.[10] It is commonly believed that compressive and tensile strains are the most important mechanical stress because they are the main component for most kinds of activities. Osteocytes transduce stress signals from bending or stretching of bone into biologic activity. It has been shown that osteocytes are more

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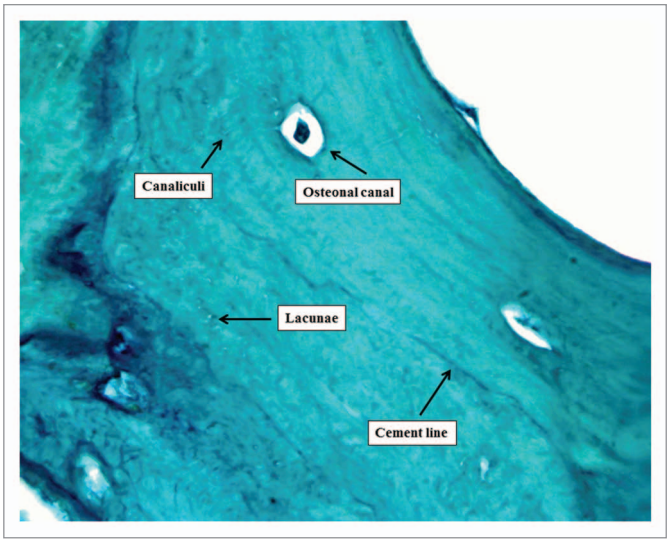


Figure 1. Compact bone microanatomy (acid fuchsin-light green staining 1,200× oil).

sensitive to mechanical stress than osteoblasts.[11] Furthermore, osteocytes are more responsive to fluid flow shear stress than to other forms of mechanical strain, such as substrate stretching.[12-14] As demonstrated, substrate stretching results in an increase of collagen or bone matrix synthesis. Indeed, bone mass and formation is increased with dynamic loading, while bone resorption is decreased. Although both tissue strain and fluid shear stress cause cell deformation, these stimuli might excite different signaling pathways related to bone growth and remodeling.

Molecular pathway involved in bone responses to mechanical strain. Mechanical strain has been reported to induce bone remodeling activity resulting in structural changes. This type of stimulation can promote the proliferation and anabolism of osteoblasts in order to facilitate bone tissue reconstruction, contributing to the homeostasis of bone tissue. In bones, mechanical stimuli are transmitted through the extracellular matrix (ECM) to osteoblasts, osteocytes, periosteal cells and osteoclasts. Osteoblasts are important mechanical receptors that can transform mechanical stimuli into biochemical signals and secrete bone matrix to promote bone matrix mineralization. Transduction of strain stress occurs at more regions of the membrane, such as intercellular junction (adherens junction) that involved cadherins (protein of adherens junctions), cell-matrix contacts called focal adhesions that involve integrins and stretch-activated channel that could respond directly to membrane perturbation.[15] Furthermore, expression of cadherins is increased by mechanical strain.[16]

Integrins, involved in focal contacts, are membrane spanning proteins that couple the cell to the extracellular environment. Functional integrins are heterogeneous dimers made of α and β subunits. In osteoblast the β_1 subunit has the predominant function role, dimerized with a subunits including α_1 through α_5. The ligands of integrins are varied, including collagen I and III and fibronectin.

Gap junctions are formed from membrane-spanning hexamers known as connexons (each subunits is called connexin) and mediate the interactions between cells. Gap junctions can pass small signaling molecules (< 1 kDa) such as calcium, inositol phosphates and cAMP.[7] Mechanical stimulation has been shown to increase expression of connexins in vitro and in vivo, suggesting that cells become better connected with their neighbors in presence of a dynamically stimulated enviroment.[17]

Moreover, alteration in ion channel activity in osteoblasts have been associated with bone cell activation trough stretch/strain stress.[18] Cyclical strain has been shown to modulate the activity of certain channels—chronically strained osteoblasts had significantly larger increases in whole cell conductance when subjected to additional mechanical strain than unstrained controls.[19] In addition to direct activation of intracellular signaling cascades, influx of a charged species such as calcium can also alter membrane potential and activate voltage sensitive channels that are not directly mechanosensitive.[20] Thus, known intracellular signal transduction pathways, such as the intracellular Ca^{2+}, Ins(1,4,5)P_3 or cAMP dependent pathways, shown to play a role in other mechanosensitive cells, are involved.

More in details, prostaglandins (PGs) and nitric oxide (NO) involved in responses of bone tissue to stress, seem to be interesting candidates for intercellular communication within the three dimensional network of bone cells as they are rapidly released by mechanical stressed bone cells.[21]

In osteocytes the mechanically induced synthesis and release of PGE2, are transmitted via the cytoskeleton which is physically linked to ions channels, as well as protein kinase C (PKC) and phospholipase A2. PGE2 mediates the gap junction intercellular communication in response to mechanical strain by increasing the number of functional gap junctions and the amount of connexin43 protein (major component of gap-junction).[22] Thus, the effect is mediated through EP2 receptors activation of cAMP dependent protein kinase A (PKA). PGE2 release due to mechanical stimulation has been reported to require a competent cytoskeleton and is increased with formation of focal adhesion and subsequent ERK and PKA signaling pathway in osteoblasts. PGE2 has been shown to have a regulatory effect on RANKL expression and therefore on osteoclastogenesis. Physiological levels of mechanical stress decrease RANKL expression and increase eNOS expression, which is mediated through ERK1/2.[21] Although the strain also activates c-jun kinase (JNK), JNK inhibitor does not prevent strain effect on either RANKL or eNOS. Reduced display of RANKL by cells present in bone downregulates the local osteoclastogenic potential. As a result of increased eNOS expression, nitric oxide (NO) is enhanced.[20]

Finally, nitric oxide is a highly reactive, easily dissolved gas released by osteocytes and osteoblasts. Nitric oxide is produced by one of three isoforms of nitric oxide synthase (NOs): nNOS, eNOS and iNOS; all three isoforms are found in bone cells, but iNOS expression has also been shown in osteoblasts but not osteoclasts. Several studies have shown that NO production rapidly increases in response to mechanical stress in bone cells. In vitro, the release of NO from bone cells in response to mechanical

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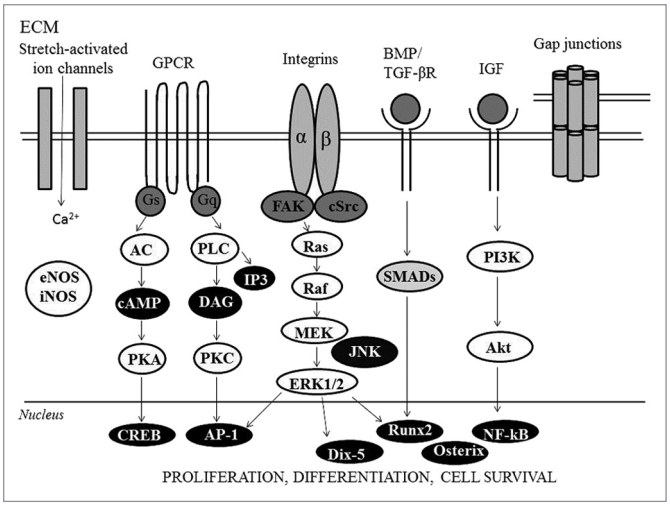


Figure 2. Schematic representation of the main molecular pathways involved in bone responses to mechanical strain.

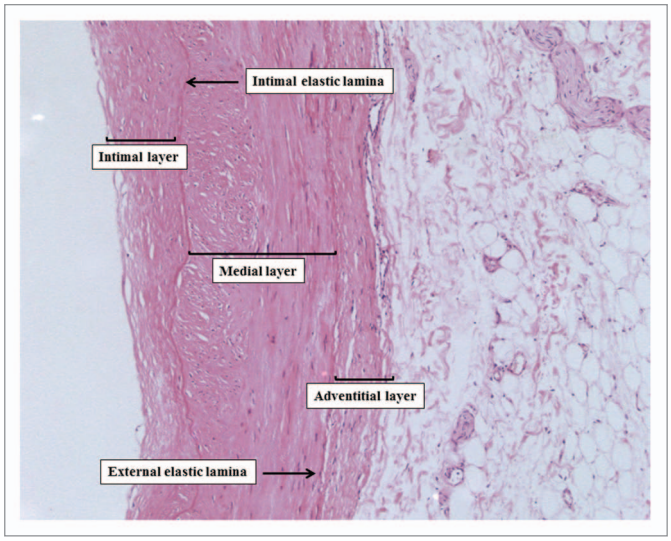


Figure 3. Blood vessels microanatomy (hematoxilin-eosin staining 430×).

stimulation has been involved in MAPK signaling, cytoskeletal adaptation and PGE2 signaling.[23]

Anyway, PGs and NO are not the only targets involved by a mechanical strain. Mechanical stimulation leads also to the upregulation of growth factors, like IGF1 (insulin-like growth factor) and IGF2, VEGF (vascular endothelial growth factor), TGFβ, BMP2 and BMP4, which act via autocrine and paracrine mechanisms through their tyrosine and serine/threonine kinase receptors. These growth factors activate PI3K/AKT, MAPK and SMAD signal transduction pathways. Phospholipase C is also activated by GPCRs, resulting in synthesis of IP3 and DAG, the latter may stimulate PKC.

In particular, the BMP2-induced signaling pathway leads to the expression of three osteogenic master transcription factors: Osterix, Runx2 and Dix5.

In particular, Runx2, a Runt domain transcription factor family member, is a master regulator of osteoblast differentiation that binds to osteoblast-specific *cis*-acting element 2 (OSE2) sites, found in the promoter regions of all major osteoblast-specific genes, including osteocalcin (OCN), osteopontin, collagen type 1, bone sialoproteins and alkaline phosphatase.[24] Runx2 forms a heterodimeric complex with its partner cbf-b and binds to DNA directly, while cbf-b modulates the affinity of the complex for DNA.[25]

The proteins and mRNAs levels, as well as the DNA-binding activity of Runx2, are increased after a low level mechanical stretching of cultured human osteoblastic cells. Runx2 activation may occur via several routes: through the interaction between ECM and cell surface integrins, through BMP, via MAPK, FGF2 and PTH signaling pathway and as a result of ATP modulation of intracellular Ca^{2+} mobilization by multiple p2 receptor. Specifically, the common target of MAPK induced by mechanical stress during osteoblast differentiation and function is believed to be the ERK pathway, which is mediated by ATP- dependent Ca^{2+} influx at calcium channel via PKC, Src family kinase, PKA, FAK and PYK2 (proline-rich tyrosine kinase 2).

Osterix (OSX) has been identified as a key transcription factor in osteoblast differentiation, which appears to be activated via Runx2-independent pathway. Both of these transcription factor regulators, Runx2 and Osterix seem to be induced early in the cellular response in mechanical strained osteoblastic cells.

Osteocytes are indeed able to respond to strain in vivo as shown by increased G6PD activity.[26] Kanno et al. shown that uniaxial sinusoidal stretching initiated the differentiation of pre-osteoblastic cells into osteogenic cells by inducing Runx2 expression in vitro[24] (**Fig. 2**).

Morpho-Functional Characteristics of Blood Vessels

Blood vessels are constituted by a three-layered structure: an intimal lining constituted by an endothelial cell monolayer, surrounded by a medial layer containing extracellular matrix (ECM) and smooth muscle cells and an outer adventitial layer consisting of connective tissue with fibroblasts. The endothelial cells (ECs) monolayer not only provides a selective barrier for macromolecular permeability between the blood and the vessel wall but also serves a number of important homeostatic functions. Indeed, ECs modulate different biological processes like vascular remodeling (growth factors), hemostasis and thrombosis (prothrombotic and antithrombotic factors), inflammatory responses (adhesion of leukocytes) and contraction of vascular smooth muscle cells (VSMCs) through the release of vasoactive substances (dilators and vasoconstrictors).[27] Instead, VSMC are highly specialized cells whose principal function is the regulation of blood vessel tone, blood pressure and blood flow distribution[28-30] (**Fig. 3**).

Blood vessels are constantly subjected to various types of hemodynamic forces, including hydrostatic pressure, cyclic stretch, and fluid shear stress. Shear stress (τ) is parallel to the vessel wall and represents the frictional force that blood flow exerts mainly on the endothelial surface of the vessel wall. Instead,

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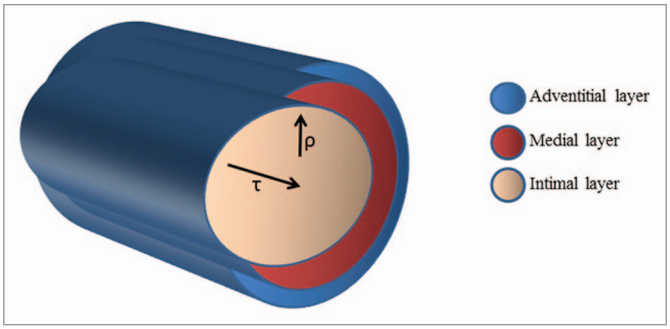


Figure 4. Mechanical and hemodynamic forces associated with blood flow: Shear stress (τ) is parallel to the vessel wall and represents the frictional force that blood flow exerts mainly on the endothelial surface of the vessel wall. Instead, cyclic stretch (ρ) is the stress perpendicular to the vessel wall and represents the circumferential deformation of the blood vessel wall during distension and relaxation of the recurring cardiac cycle.

cyclic stretch (ρ) is the stress perpendicular to the vessel wall and represents the circumferential deformation of the blood vessel wall during distension and relaxation of the recurring cardiac cycle (**Fig. 4**).

Mechanical or hemodynamic forces associated with blood flow play a central role in the homeostasis of the circulatory system. These forces act on the vascular wall, contributing to the regulation of myogenic tone, responses to vasoactive molecules, gene regulation, vascular permeability and remodeling. Disruption of normal hemodynamic loading can be responsible of the development of vascular diseases, including hypertension, thrombosis, aneurysms and atherosclerosis. While physiological cyclic stretch induces cell cycle arrest in VSMC, chronically increased blood pressure and vascular transmural stress activate vascular cell proliferation (eventually leading to luminal stenosis), collagen and fibronectin synthesis which results in thickening of the vascular wall as a feature of hypertension-induced vascular remodeling,[31,32] finally altering arteries compliance. Although vascular endothelial cells and vascular smooth muscle cells are exposed to both types of mechanical forces, the shear stress resulting from blood flow is sensed mainly by ECs, whereas SMCs are primarily subjected to cyclic stretch resulting from pulsatile pressure. Vascular cells are equipped with numerous receptors that allow them to sense stimuli such as strain, pressure and fluid shear stress and transduce these mechanical signals into a biological response through a process named mechanotransduction. The cytoskeleton and other structural components have an established role in mechanotransduction, being able to transmit and modulate tension within the cell via focal adhesion sites, integrins, cellular junctions and the extracellular matrix. Measurements of circumferential cyclic strain in vivo average 2% in the human thoracic aorta at a frequency close to 1 Hz with increases upwards of 30% strain on arterial walls in hypertension.[33] The effects of cyclic strain on cell mechanobiology depend on rate, duration and species. Cyclic strain mediates the ability of ECs to remodel their ECM, proliferate, change shape, and signal to SMCs. Cyclic strain induce also ECs proliferation, morphological alignment and change in gene expression with consequences for cell phenotype and vessel wall homeostasis. In the second part of this section, more details of the molecular mechanisms involved will be discussed.

Molecular mechanisms involved in vascular responses to mechanical strain. Although blood flow imposes shear stress on the endothelial cells, cardiac pulsation generates circumferential stretch and impose mechanical stimulation on both endothelial and SMC. Mechanical stimuli need to be converted in biochemical signal in order to activate transcription factors and finally modulate gene expression. In fact, mechanical stretch on vascular cells has significant effects on the expression of genes related to vascular remodeling and cell functions such as cell proliferation, apoptosis, migration and control of cell phenotype. For instance, phenotypic responses of vascular cell exposed to cyclic stretch in vitro include increased expression of contractile and cytoskeletal proteins (myosin light chain kinase, smooth muscle myosin heavy chains and desmin).[34] A number of bioactive proteins regulated by cyclic strain have been also identified in endothelial cells and they include IL-8, TGFβ, FGF2 and VEGF.[35,36]

The mechanochemical transduction involves the activation at the cell membrane surface of specific mechanosensors and the related intracellular signaling pathways.[37] Thus, an intact cytoskeleton is important for the stretch-induced adjustments in vascular cells.[38] SMCs express many different receptors and ion channels, which can be activated by mechanical stress leading to the activation of multiple classic signaling pathways, such as G protein, kinases, calcium, cAMP, nitric oxide (NO), eNOS, MAPK and MKP-1. Moreover, mechanical stresses appeared simultaneously to initiate multiple signaling pathways.

In particular, integrins form a signaling interface between the extracellular matrix (ECM) and the cell. These proteins participate not only to cell attachment to the substrate but also to intracellular transmission of mechanical signal. Mechanical stresses stimulate conformational activation of cell integrins and increase cell binding to extracellular matrix. The dynamic formation of new ligand-integrin connections is required for stretch induced mechanotransduction. During the stimulation of vascular cells by mechanical factors such stretch, several signaling events are associated with the formation of focal adhesion, which comprise integrin cluster and cytoskeletal protein. The proteins present at focal adhesion become phosphorylated on tyrosine when the cells are stimulated, a FAK activation is an indicator in focal adhesion formation.[39,40] Up cell attachment to ECM proteins, integrins became activated and form cluster at the cell surface thus initiating the formation of adhesion complexes which will enhance FAK's catalytic activity and increase FAK tyrosine phosphorylation. FAK phosphorylation at tyrosine 397 (Y^{397}) leads to the recruitment of Src and Src-family kinases as well as to an increased phosphorylation of other proteins present in the adhesion complex such as paxilin and p130Cos.[41,42] Subsequent phosphorylation of specific tyrosine residues leads to the recruitment of additional SH2-domain-containing signaling proteins such as PI3K and Grb2.[43] Among all integrin receptors, integrin $\alpha_5\beta_3$ has been identified as having particularly interesting expression pattern among the vascular cells during angiogenesis and vascular

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remodeling.[44,45] In particular, integrin $\alpha_5\beta_3$ binds numerous ECM ligands with exposed RGD peptide as fibronectin, vitronectin, fibrinogen and is involved in responses to mechanical strain. In the '90s Wilson and colleagues established a link between the mechanical stimuli and the action of growth factors. Their studies demonstrated that cyclic stretch increased VSMC proliferation when they are plated on collagen, fibronectin or vitronectin, but not on laminin or elastin; further, these effects required the production of PDGF suggesting a tight interaction between integrins and growth factors downstream signaling pathways related to mechanical stimuli.[46] Generally, growth factors receptors belong to two classes of membrane proteins: tyrosine kinase receptors and G-coupled receptors and G proteins.

There is still another membrane structure which is involved in mechanosensing: ion channels. VSMCs stimulated by mechanical stress result in a transient increase in intracellular calcium and divalent cations and depolarization which maintain smooth muscle tension. Opening these channels causes Ca^{2+} and Na^{+} influx and membrane depolarization, which contributes to the myogenic response to mechanical stretch.[47] The altered stretch-activated channels in arterial SMCs may contribute to the enhanced myogenetic responses as well as the generation of hypertrophy and remodeling of arterial tissue in hypertension.

All the cited membrane mechanosensors have a common intracellular pathway often converging to the MAP kinase signaling. The MAP kinase comprises a ubiquitous family of threonine/tyrosine kinases, and includes extracellular signal-regulated kinases (ERK), stress activated protein kinases (SAPK) or c-Jun NH2-terminal kinases (JNK) and p38/ERK kinases.[48-50] This cascade is an important pathway whereby signal originating from mechanical forces can lead to gene expression and protein synthesis. More in details, this pathway implicates the sequential phosphorylation and activation of the cytoplasmic protein kinases MEKK, MEK and finally MAP kinase. The MAP kinase cascade comprises three different pathways. Phosphorylation of a MAP kinase, which lies downstream of the MEKK Raf and is present in two isoforms termed ERK 1 and 2, leads to the activation of regulatory proteins both in the cytoplasm and the nucleus. A second branch of the MAP kinase family, termed stress-activated protein kinases (SAPK) because they are activated by UV light, heat shock, hypoxia or high osmolarity, includes kinases that phosphorylate the N-terminal of transcription factor c-jun (JNK). Finally, a third branch comprises p38, also activated by osmotic stress.[51]

Related to mechanical strain, a cyclic stimulus activates both ERK1/2 and JNK in VSMC.[52] Moreover, it induces on vascular smooth muscle cells (VSMC) alignment and differentiation.[53,54] The signaling pathway involved in cells alignment includes p38, MAPK (mitogen-activated protein kinase), NO (nitric oxide) and ROS (reactive oxygen species).[54-56] and the mechano-sensor mainly involved is integrin β_1.[55] Moreover, cyclic strain increases both smooth muscle α-actin protein expression and promoter activity. The induction of smooth muscle α-actin is mediate by activation of JNK and p38 MAPK pathway.[57] Thus mechanical strain leads to migration, proliferation and contraction. The primary genes encoding SMC contractile proteins are regulated by stretch-induced RhoA pathway and associated transcription factors.[58] Moreover, mechanical stress regulates VSMC migration trough ERK1/2 and MLCK (myosin light-chain kinase).[59] Also p38, MAPK and TGFβ_1 are involved in migration of VSMC after mechanical stress. In fact, inhibition of p38 MAPK and TGFβ_1 activity decreases migration activity.[60]

The effects of mechanical strain on cell survival and proliferation are mainly related to $\alpha_5\beta_3$ integrin expression, stabilization of PINCH1, a survival protein that is linked with integrine and the cytoskeleton.[61] siRNA (small interfering RNA) against intregrin β3, abolished the anti-apoptotic effect of mechanical stress. Also downregulation of Rho inhibits the proliferation of VSMC induced by stretch.[58] While, the proliferation of VSMCs induced by mechanical stretch is mediate by the activation of IGF-1 (insulin growth factors 1) and IGFR-1 (receptor). Anyway, mechanical stress induces apoptosis in differentiated VSMC, but not in proliferating VSMCs and the stretch-induced apoptosis in VSMC is associated with BAD expression. VEGF and overexpression of the anti-apoptotic protein bcl2 decreases the expression of BAD and apoptosis induced in response to stretch.[38]

Finally stress strain also mediates vascular remodeling. The signaling involved in response to mechanical stretch includes ROS, NO, NFκB, EGFR, MAPK and PKC. Mechanical force can be transduced via ROS-dependent autocrine and paracrine EGFR activation, and may regulate VSMC proliferation and synthetic activity through the NFκB pathway.[62]

Anyway, using cells from different species and modifications in type (cyclic or steady), intensity and duration of stretch may cause the different biological effects in vitro. For instance, cyclic but not steady mechanical strain activates vascular FAK, and Src and integrins are involved in steady pressure-induced FAK activation in the vessels.[42]

Moreover, low (5%) or high (18%) magnitude cyclic stretch selectively involve small GTP-ases (Rac and Rho respectively) with direct consequence on actin polymerization and stress fibers formation[63] (**Fig. 5**).

The Heart

Cardiac tissue is exposed to dynamic mechanical stresses from the early development for all lifetime. Mechanical forces are transduced into biochemical and electrical responses through the mechanotransduction process. In the heart, this process is mediated by the cardiomyocytes, originating from cardiac progenitors, which represent the fundamental mechanical work unit of the heart. In normal myocardium, cardiac myocytes are cylindrical structures elongated and aligned along a longitudinal cellular axis, with the aim to facilitate a fast propagation of the electrical impulses and the uniaxial alignment of sarcomeres, both of which contribute to a contraction at regular intervals. Heart chamber filling and wall distension within diastole account for rapid changes in pressure and volume that are released by the wave of contraction that pumps blood through the body. At the cellular level, these pulsatile stimuli are experienced as cyclic strains (relative deformation) and stresses (force per unit area). In the heart, myocytes are subjected to strain in diastole before contraction

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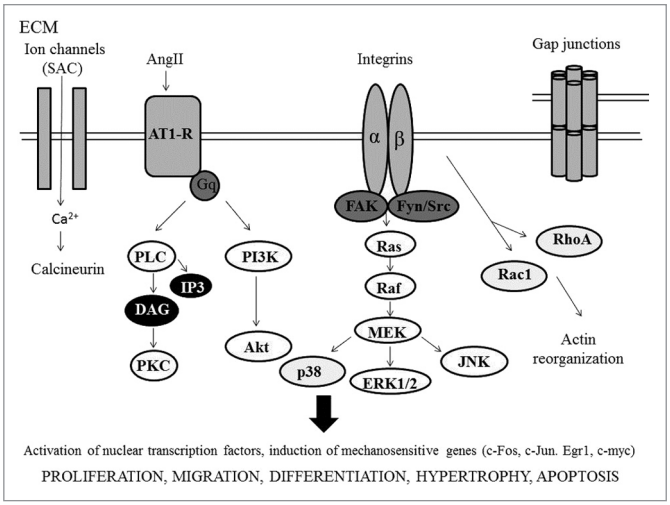


Figure 5. Main molecular pathways involved in mechanotransduction in vascular cells.

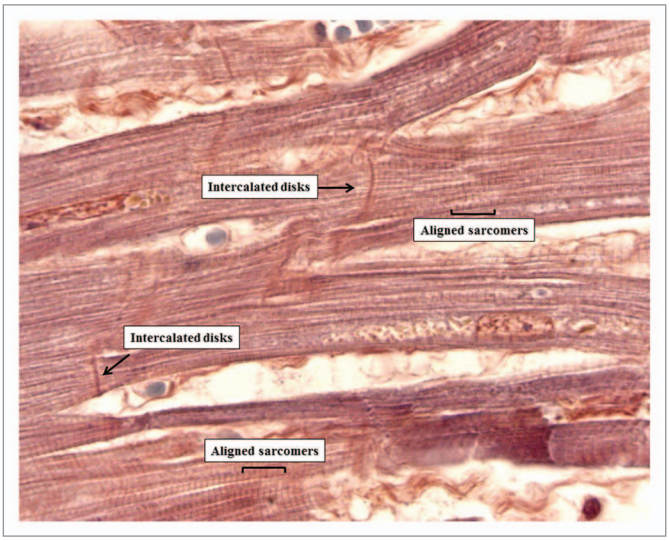


Figure 6. Heart microanatomy showing the intercalated disks (Phosphotungstic acid hematoxylin staining 1,200× oil).

(preload) and actively contract against imposed load in systole (afterload). Cardiac myocytes are primarily subjected to cyclic stretch due to pressure and volume overload.[38] It has been shown that cardiomyocytes respond to mechanical forces promoting cardiac hypertrophy and development, adaptative remodeling and changes in gene expression.[64,65] In fact, stretch of cardiomyocytes cause transcriptional activation of gene like atrial natriuretic factor (ANF), skeletal α-actin and β-myosin heavy chain (MHC).[65] Mechanical stimuli can also affected cytoskeletal and sarcomeric organization to regulate cell shape and alignment changes in contractile performances.[66,67] Dysregulation of mechanical signaling can cause cardiac remodeling, characterized by cardiomyocytes loss, interstitial fibrosis and collagen deposition, leading to heart failure, myocardial infarction and cardiomyopathies.[68] In both normal and pathological conditions, the cardiomyocytes cytoskeleton play key role in sensing mechanical stress and mediating structural remodeling and functional responses within the myocytes. Mechanical stimuli are sensed by protein complexes associated with the sarcomeres in order that actin filaments slide along the adjacent myosin filaments promoting the cardiac contractile forces. Let's go further in the molecular mechanisms involved in cardiac tissue mechanostransduction (**Fig. 6**).

Cardiac tissue mechanotransduction. Mechanical stresses can deform the ECM and alter integrin structure leading to activation of second messenger pathway. Several mechanoreceptors are involved in mechanical stress. In particular the interaction between cardiomyocytes and ECM involved mainly integrins. The cardiac ECM is a dynamic entity, it is composed of basement membrane adhesion proteins such as fibronectin, collagen type IV, laminin and proteoglycans.[69] Integrins can be a mechanosensor that transmits mechanical signal to the cytoskeleton. The cardiomyocytes express a variety of α subunits; however, they primarily express β1-integrins. Integrins connect to actin through linking proteins such as talin, vinculin and α-actinin, but also with the N-terminal domain of focal adhesion tyrosine kinase (FAK), are also associated with signaling molecules such as small GTP-binding proteins Rho, Rac and Cdc42.[70] Vinculin is a crucial downstream effectors of myosin VI in E-cadherin-mediated adhesions. Vinculin plays a crucial role in cardiomyocytes mechanotransduction and is found at costameres as well as in the intercalated disk.[71] However several proteins interact with FAK, such as Src, Fyn, p130^{cas}, Graf, Grb2 and PI-3-kinase. These signaling molecules further activate various downstream protein kinase cascades, including p21^{ras}, mitogen-activated protein (MAP) kinase, protein kinase C (PKC) and p70^{s6k}. Intercellular communication is via the intercalated disk. Intercalated disc is made largely of desmosomes, gap junctions and adherens junctions. Desmosomes are particularly abundant in tissues such myocardium. Desmosomal adhesion molecules, desmocollin and desmoglen are members of cadherins family of calcium-dependent adhesion molecules.[72] Gap junctions connect the cytoplasm of neighboring cells allowing the passage of small molecules (1,000 kDa) and electrical current, in fact connexins form diffusion pores. Each gap junction is formed by two connexons, each of which is made of six identical or different proteins called connexins. Myocardial gap junction are composed of three connexin isotopes: connexin 40 (Cx40), connexin 43 (Cx43) and connexin 45 (Cx45), the most abundant isoform (43 is molecular weight in kDa) is upregulated after mechanical stress in cultured rat neonatal cardiomyocytes.[73] This increase in Cx43 expression corresponded to an increase in conduction velocity, and appears to be mediated by vascular endothelial growth factor (VEGF). AngII, VEGF and TGF-β may mediate the stretch-induced Cx expression. Gap junctions via actin are connected to integrins. Adherens junctions (fascia adherens junction) are composed mainly of N-cadherins, homophilic Ca^{2+}-dependent cell-cell adhesion molecules. Cadherins activate the pathway of α-catenins and β-catenins.[74,75] These mechanotransductions play an important role in maintaining the structural and mechanical organization of cardiac tissue during and after development.[76] The sensing of mechanical stress is realized via stretch activated

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ion channels (SAC). Typically stress-activated channels (SAC) allow the passage of cation K^+, Na^{2+} and Ca^{2+}.[76] Another mechanical sensor is titin (called connectin). Titin, an intracellular protein necessary for sarcomeric structure, contributes significantly to the mechanical properties of the sarcomere. Titin runs from the Z-disk to the M-band where bounds myosin, is involved in response to stress.

Downstream to the mechanosensors activation, several studies show that MAP kinase constitute major stress-activated signal pathway in cardiomyocytes.[77] Mechanical stress of neonatal cardiac myocytes has been shown to activated ERK1 and ERK2 and their downstream protein kinase pp90 rsk, also activates the upstream regulators of ERK including MAP kinase kinase (MEK1) and MAP kinase (Raf1).[78] Also c-Jun N-terminal kinases (JNK) can be activated by mechanical stress.[79]

Mechanical stress causes activation of phospholipases, for example activation of phospholipase C (PLC). Phospholipases generate lipid-derived second messagers such as inositol-1,4,5-trisphospate (IP3) and diacylglycerol (DAG). DAG, a soluble molecule, causes Ca^{2+} release that activates protein kinase C (PKC).

Ultimately, mechanical stress activates intra-nuclear factors such as the serum response factors (SRE)-p&2 TCF complex via SRE, causing induction of c-*Fos*. SRF is a transcription factor that regulates many adhesion-related genes, and is regulated by a number of independent pathways. The first group of genes activated by mechanical stretch is immediate early genes such as *c-Fos*, *c-Jun*, *Egr1* and *c-myc*.[80] Pathological levels of mechanical stress activate nuclear transcription factors like NFκB mediated by VEGF.[81]

Furthermore, mechanical stress induces autocrine or paracrine secretion of growth factors. Presence of growth factors is one of the important mechanisms in the pathogenesis of stretch-induced organ hypertrophy.[82] After mechanical stress, cardiac myocytes synthesize growth factor like angiotensin II, endothelin 1 and basic FGF (fibroblast growth factor). Mechanical stress at physiological level does not induce damage of cardiac myocyte, but levels of pathological mechanical stress can induce apoptosis. It's what happens in certain diseases such as hypertrophic cardiomyopathy. Altered mechanical stress associated with myocardial infarction leads the constitutively production of cytokine such as tumor necrosis factor α (TNF α), interleukin 1 (IL1) and IL6 via the MAPK and JAK-STAT pathways. These pathways activate nuclear transcription factor like NFκB and AP-1 that encode for TNF α and IL6.[83] These levels of cytokines increase metalloprotease MMP activity such as MMP2 and MMP9 in local matrix. Moreover, pathological levels of mechanical stress induce ROS production stretch-amplitude-dependent.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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