[Frontiers in Bioscience E1, 189-199, June 1, 2009]

Calcium and the mechanotransduction in cardiac myocytes

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1. ABSTRACT

Mechanical stress is a major triggering stimulus for the installation of cardiac hypertrophy as well as for the structural and functional deterioration occurring in the hypertrophy decompensation. The sensing of mechanical forces and their conversion into biochemical signals depend on the integrity of subcellular structures such as the costameres and Z-disks. Signaling molecules concentrated into these structures are thought to be activated by the stress-induced deformation of structural proteins. Evidence also indicates that Ca^{2+} may be involved in mediating the mechanical forces conversion into biochemical signals and biological responses. Ca^{2+} channels, transporters and activated proteins are concentrated at the junctions between the T-tubules and the sarcoplasmic reticulum which are in close proximity to the costameres and Z-disks. This provides a structural basis for the influence of mechanical forces on Ca^{2+} transport and on the events related to signaling molecules clustered in the costameres and the Z-disks. Emerging data reviewed here are providing insight into how Ca^{2+} and mechanical mediated signaling are coordinated to modulate the functional and trophic responses of cardiac myocytes to mechanical stress.

2. INTRODUCTION

Cardiac myocytes are constantly exposed to forces resulting from the hemodynamic load and from their own contractile activity. Such forces are the primary determinants of the size and mass of this particular cell type either under normal or increased demand. Typically, sustained increase of mechanical forces induces the cardiac myocytes to enlarge in consequence of the deposition of sarcomeric units, mitochondria and other organelles. A prevailing current view is that such changes result mainly from the modulation of transcriptional and translational processes coordinated by growth related intracellular signaling pathways activated by mechanical stress-sensing molecules. One potential signaling system that has been implicated in the responses of cardiac myocytes to mechanical stress is the calcium (Ca^{2+})-regulated proteins. In this review we discuss the connections of Ca^{2+} signaling with the mechanisms underlying the mechanotransduction in cardiac myocytes.

3. MECHANOTRANSDUCTION IN CARDIAC MYOCYTES

This topic will summarize the general aspects of mechanotransduction pertinent to the discussion of Ca^{2+}

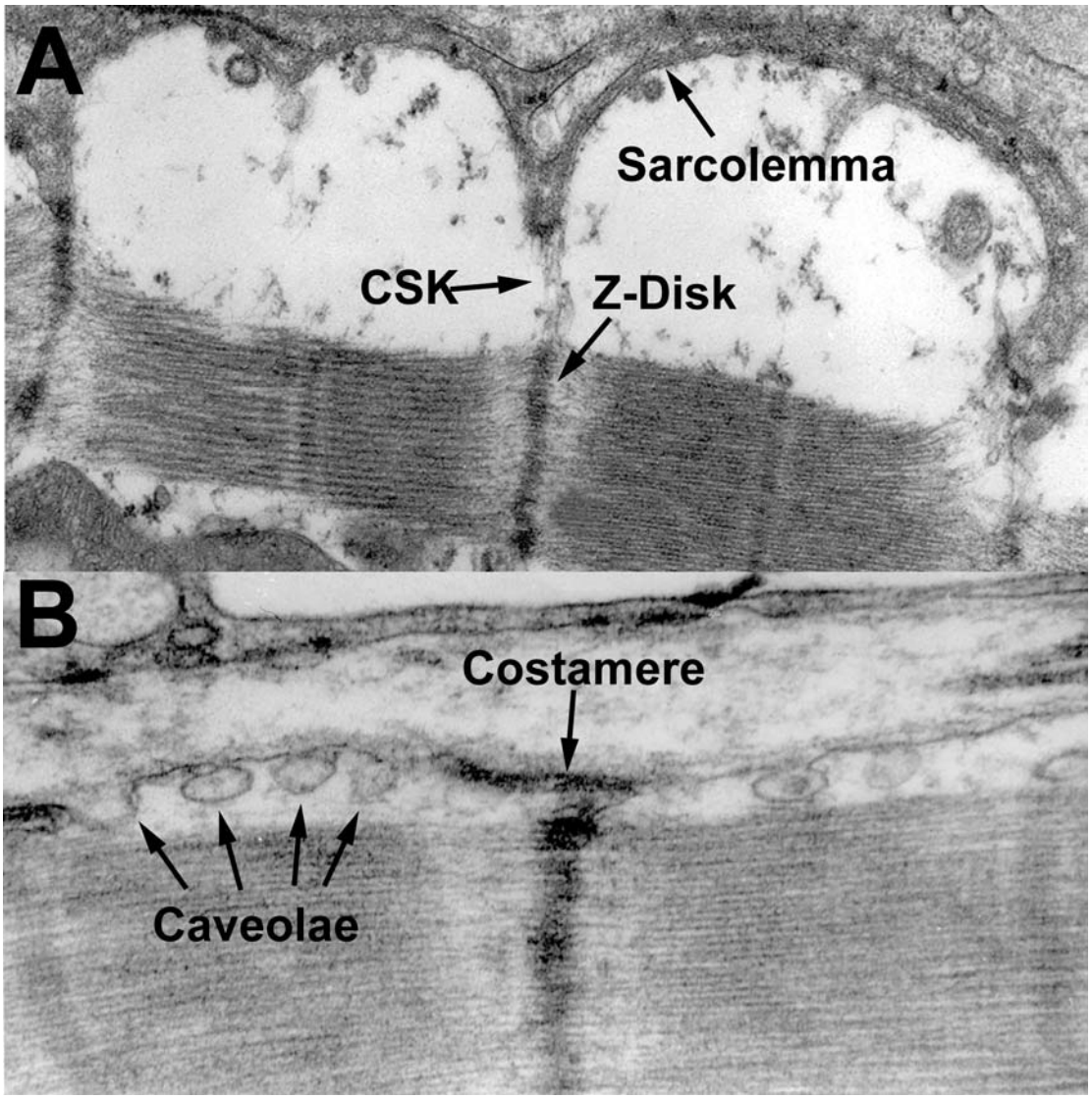

Figure 1. Costamere and caveolae in cardiac myocytes. A. Electron micrograph from a longitudinal section of rat ventricular myocyte shows the costamere region. The sarcolemma and the Z-disk are connected by filamentous proteins in the costamere. B. The longitudinal section of rat ventricular myocyte shows several caveolae in the sarcolemma nearby the costamere. CSK: cytoskeleton.

signaling elicited by mechanical stress in cardiac myocytes. Several excellent reviews on mechanotransduction in cardiac myocytes are available, and should be consulted for additional details and perspectives (1-5). Although there has been a rapid progress in our understanding of cardiac myocytes responses to mechanical stress, the molecular mechanisms of mechanotransduction in this particular cell type are still not well understood. An emerging body of evidence, however, supports the notion that the mechanotransduction may take place at specialized subcellular sites such as costameres and Z-disks which are otherwise interconnected.

Costameres are rib-like bands that encircle the cardiac myocytes perpendicular to its long axis and flank the Z-disks (1, 6). As shown in the Figure 1, it consists of a complex protein network that forms a physical attachment of the underlying outer Z-disk to the surrounding extracellular matrix. The Z-disk forms the border of individual sarcomeres, where opposing thin filaments and individual titin molecules are interdigitated and cross-linked by α-actinin dimers. In addition to these proteins, a large number of novel molecular components of the Z-disk have been recently reported. Proteins such as CapZ, obscurin, γ-filamin and non-sarcomeric myosin II seem to contribute to stabilize the complex structure of the Z-disks, while others such as muscle LIM protein (MLP), PDZ/LIM proteins, myotilin, myopaladin, and Cypher/ZASP/Oracle are possibly anchoring proteins which are intermingled with the network of structural proteins. Some of the anchoring proteins are multidomain molecules capable of interacting with structural as well as signaling molecules

such as kinases, phosphatases, and Ca^{2+} binding proteins (1-3, 7). Mechanically induced conformational switches of the structural proteins are suspected to favor the recruitment and activation of the signaling molecules by the anchoring proteins thereby converting mechanical stimuli into biochemical signals. Consistent with this model, single-molecule studies have revealed that mechanical forces can regulate conformational changes of molecular recognition sites or the exposure of cryptic binding sites (8). However, the influence of mechanical forces in the costameres or Z-disk specific structural proteins remains largely unexplored.

Most of the experimental evidence that either costameres or Z-disks play a role in the mechanotransduction in cardiac myocytes come from studies performed in models in which the key structural, anchoring or signaling molecules were deleted or had their function impaired. For instance, disruption of β1 integrin, a key transmembrane costameric protein results in intolerance to hemodynamic overload (9). Further, deletion or impairment of FAK, a mediator of signals elicited by integrin, has also been shown to compromise the responses of cardiac myocytes to mechanical stress (10-12). Notably, the activation of FAK by mechanical stimulation in cardiac myocytes seems to be dependent on its clustering at the costameres and Z-disks (10, 13). The stretch-induced rearrangement of the cytoskeletal proteins at or near the costamere and Z-disk may direct the assembly of a multicomponent signaling complex that include, in addition to FAK and Src, adaptors and docking proteins. This rearrangement is suspected to be promoted by a combination of integrin clustering and activation of RhoA/ROCK signaling pathway (10, 14). At sarcomeric regions, FAK also co-localizes and interacts with the tail of myosin heavy chain (13). Recent work showed that FAK silencing prevented as well as reversed load-induced hypertrophy, while preserving the LV function despite the persistent pressure overload (15).

More recently, ILK which is also downstream to integrin has received attention as a critical intermediate in the signaling process activated by mechanical stress in cardiac myocytes (16). Similarly, PYK2, a tyrosine kinase from FAK family, acts as an important scaffolding protein downstream to integrin and has been reported to be highly expressed and phosphorylated in overloaded cardiac myocytes (17).

In addition to integrins, costameres are enriched in dystrophin that has also been implicated as a structural molecule involved in the ability of cardiac myocytes and skeletal muscle to the mechanical stress response (18, 19). Dystrophin is tightly attached to the sarcolemma and to costameres by interacting with the integral membrane dystroglycan and the subsarcolemmal dystrobrevins and syntrophins and to γ-actin filaments of costameres (18, 20, 21). These connections seem to stabilize the sarcolemma against physical forces transduced through costameres during muscle contraction or stretch. Accordingly, in human and mice Duchene muscular dystrophy, the impairment of dystrophin leads to a disorganized costameric lattice and disruption of sarcolemmal integrity (22).

As to the case of the costameres, deletion of structural proteins related to the Z-disks also affects the ability of cardiac myocytes to adequately respond to mechanical stress. Deletion of the MLP anchoring protein was demonstrated to be accompanied by extensive disarrangement of the Z disk and lack of proper response to mechanical stress (23). Interestingly, in addition of interacting with structural proteins of the Z disk and sarcomere, MLP was found to interact with calcineurin which is known to elicit hypertrophy linked to Ca^{2+} signaling (24, 25). MLP knockout mice have been shown to lack an appropriate stretch-induced release of brain natriuretic factors, implying MLP in the mechanisms mechano-sensing in cardiac myocytes (23).

Recent evidence indicates that titin may function as a key biomechanical sensor. Signaling processes linked to titin and potentially involved in the mechanotransduction have been demonstrated in the titin regions near the Z-disk, in the central I-band and the M-line (26). The Z-disk titin-capping protein T-cap, or telethonin, binds to titin's N-terminus and links titin to signaling and structural molecules (27, 28). T-cap interacts with cytoplasmic domains of two membrane associated proteins, the K^+ channel subunit minK/isk in the T-tubules and small ankyrin-1 (sANK-1), a transmembrane sarcoplasmic reticulum (SR) protein (29, 30). The minK/isk interaction may function to modulate K^+ channel opening in response to stretch while the sANK-1 interaction may serve to fix the position of the SR around the Z-disk. Furthermore, in its N-terminal portion, titin has a serine-threonine kinase domain (TK) predicted to be activated by mechanical stimuli. Two hybrid system assays showed the zinc-finger protein nrb1 as a TK ligand and this association has been described as essential for the correct positioning of p62 (a scaffold protein) and MuRF2 (another zinc finger protein) at M band. Under mechanical stress, there is a dissociation of the TK-associated proteins and MuRF2 accumulates in the nucleus. The MuRF2 protein is a partner of the SRF transcription factor that plays a crucial role in immediate early genes activation in response to hypertrophic stimuli. These data indicate that titin may act as sensor and responsive protein to mechanical stress, connecting the sarcomere to the modulation of transcription in cardiac myocytes (31).

Although these data indicate that the structural integrity of the costameres and Z-disks and the clustering of signaling proteins in these sites are necessary for an appropriate response of cardiac myocytes to mechanical stress, the understanding of how mechanical stress activates signaling events remains unresolved.

4. SPATIAL ORGANIZATION OF Ca^{2+} SIGNALING IN CARDICA MYOCYTES

Calcium regulates cellular processes by acting as a messenger that interacts with and modifies the function of key Ca^{2+}-regulated proteins. The efficiency of Ca^{2+} as an

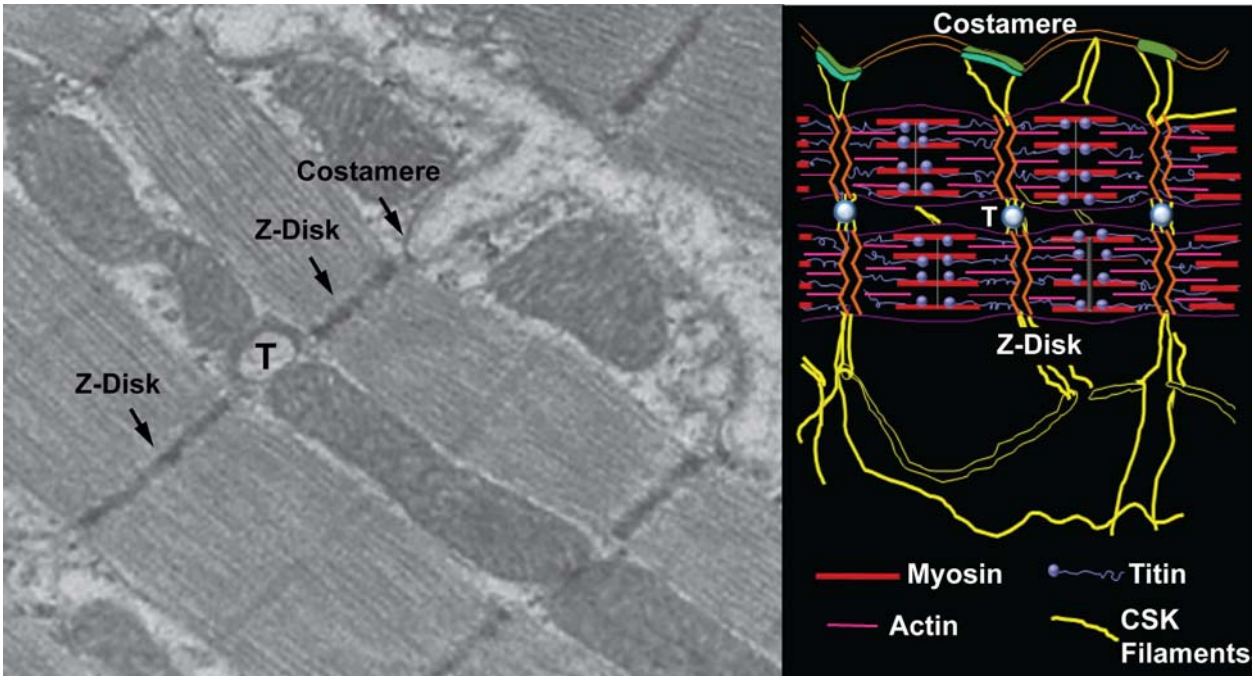

Figure 2. Structural base for the interaction between mechanical stress and Ca^{2+} signaling. A. A thin section electron micrograph from rat ventricular myocyte that illustrates the typical structure relationship between the T-tubules (T) with Z-disks and costameres. B. Diagram of the close apposition of T-tubules (T), Z-disks and costameres, interconnected by filamentous proteins from the extrasarcomeric cytoskeleton (CSK).

intracellular messenger depends on its localized and finely regulated delivery to specific sites of the cell (32). Localized Ca^{2+} signaling events have been generally defined as Ca^{2+} microdomains (33). This process is carried out in spatially organized microenvironments which comprise so far membranes, regulatory proteins, ion channels, transporters as well as downstream Ca^{2+} target proteins. In cardiac myocytes such assembly of proteins and Ca^{2+} stores are mainly located at the junction of the T-tubules with the sarcoplasmic reticulum (SR), where Ca^{2+} plays a major role in regulating the contraction. In ventricular cells the T-tubules and the junctional zones are lined up alongside the Z-disks (Figure 2) (34, 35). In such zones, ryanodine receptors lie close to a portion of T-tubule that is enriched with Ca^{2+} L-type channels (36). The opening of these channels induced by changes in transmembrane electric potential creates a localized Ca^{2+} influx which then triggers the opening of the ryanodine receptor and the release of large amounts of Ca^{2+} from SR stores. In addition to Ca^{2+} L-type and ryanodine receptors, other proteins related to Ca^{2+} handling (e.g. Na^{+}-Ca^{2+} exchanger - NCX) are more concentrated in the T-tubules than in the surface membranes (34).

Key proteins involved in the modulation of cardiac function and trophism are clustered at or in the proximity of the T-tubules, including nitric oxide synthase type 3 and cAMP-dependent pathway proteins, such as the ß-adrenoceptor, G_s, adenylate cyclase, and AKAP (37-41). Interestingly, the protein phosphatase calcineurin, appears to be colocalized with protein kinase A (PKA) near the T-tubules (42). In addition, many key components of major signaling pathways (e.g. mitogen-activated protein kinases) are found predominantly at cellular regions close to the T-tubules, organized in multimolecular complexes named as signalosomes (32, 43). These complexes are thought to integrate upstream signals mediated by mechanosensors, receptors to agonists (e.g. adrenergic neurotransmitters, angiotensin II) or Ca^{2+} and to control downstream effectors.

In addition to the junctional zones, signaling complexes and Ca^{2+} handling proteins have been demonstrated to compartmentalize in the caveolae, which are regions of membrane invagination that occur in great number, but not exclusively in the T-tubule sarcolemma (Fig 1B) (44-47). The compartmentalization of signaling complexes in the caveolae seems to be mainly dependent on the ability of caveolin to assemble proteins via its N-terminal scaffolding domain. Several signaling molecules including G protein α subunits, adenyl cyclase, PKA, Ras, and eNOS were demonstrated to be clustered by caveolin. Moreover, other proteins that are critical downstream effectors of Ca^{2+} signaling, such as AKP, PKC, CaMKII have been shown to cluster in the caveolae, where they interact with docking proteins and ion channels (48-51).

More recently, some signaling events mediated by Ca^{2+} have been shown to depend on a change in the nuclear Ca^{2+}. For instance, the phosphorylation of histone deacetylase 5 (HDAC5) induced by the hypertrophic agonist endothelin appears to be regulated by an IP3-dependent release of Ca^{2+} in the vicinity of the nucleus (52). The normal global Ca^{2+} signals that spread through the cytoplasm and nucleus were not able to activate the

CaMKII responsible for stimulating the phosphorylation of HDAC5, indicating that highly localized microdomain of Ca^{2+} in the immediate vicinity of the IP3 receptor may be responsible for the phosphorylation of CaMKII. Although this was demonstrated to endothelin, it might be well possible that such process will be responsive to mechanical stimuli. Indeed, there is a clear line of force communication from the extracellular matrix to intracellular cytoplasmic structures. Nuclear structure and mechanics are gaining recognition as important factors that affect gene expression, development, and differentiation in normal function and disease (53).

Therefore, an emerging view implies that there is an extensive toolkit of Ca^{2+} signaling components organized in compartmentalized microenvironments (signalosomes) which deliver Ca^{2+} signals with spatial and temporal characteristics dictated by the type of stimulus that might be periodic depolarization, mechanical stress, and agonist mediated-receptor activation (32). Changes in the properties of the Ca^{2+} delivery carry information to signaling pathways coupled to Ca^{2+} signalosomes, while modifications in the activity of the related molecules may also reciprocally modify the efficiency of Ca^{2+} signaling. Further, the expression of Ca^{2+} signaling components can be altered to compensate for long-lasting alterations in the signaling pathway. Interestingly, there are data indicating that the transcription of Ca^{2+} toolkit components may be commonly under the control of the transcription factor NFAT, which is itself controlled by Ca^{2+} signaling, implying, therefore, a complex feedback regulation (54, 55).

5. A STRUCTURAL BASIS FOR MECHANICAL STRESS AND Ca^{2+} SIGNALING INTERACTION

The proximity of the T-tubules to the Z-disks and costameres (Fig 2) suggests that the processes involved in the mechanotransduction as well as in the Ca^{2+} signaling may share a common pool of downstream signaling protein complexes. Such structures are mechanically coupled by a common scaffold of the extrasarcomeric cytoskeletal protein meshwork, providing a structural base for the influence of mechanical forces on Ca^{2+} signaling as well as the modulation of signaling mechanisms activated by mechanical stress by Ca^{2+} (56). Accordingly, data are emerging indicating that signaling processes arising from the costameres modulate or are modulated by Ca^{2+} signaling. The increase in Ca^{2+} induced by stretch in cardiac myocytes might be related to integrin stimulation. It has been shown that activation of integrins by RGD peptide modulates RyR2 in cardiac myocytes through locally released NO, an effect probably mediated via FAK-induced NOS activation (57). However, it remains undefined whether this mechanism is activated in response to mechanical stress. Moreover, PYK2, a signaling kinase downstream to integrin which seems to be an essential component in the hypertrophic responses of cardiac myocytes, has been shown to undergo activation by a complex interaction of integrin engagement and increased intracellular Ca^{2+} (17, 58-61).

Dystrophin is suspected to be involved in regulating L-type Ca^{2+} and SACs - stretch-activated (62-64). It is hypothesized that when cardiac myocytes are stretched, the opening of SACs is limited by dystrophin regulation. However, in the absence of dystrophin the activities of L-type Ca^{2+} channel and SACs become greater and promote an entry of Ca^{2+} into the myocytes (65, 66). In line with this, the lack of dystrophin is accompanied by an abnormal Ca^{2+} handling in cardiac and skeletal myocytes resulting in the rise of resting $[Ca^{2+}]_I$ that is suspected to contribute to the damage of the dystrophic myocytes. Another possibility for Ca^{2+} entry pathway could be related with small tears in the membrane as was demonstrated in myocytes from dystrophic mdx mice. In this work, the L- type Ca^{2+} channels were blocked and did not avoid $[Ca^{2+}]_I$ increase resulting from stretch. Otherwise, the application of a membrane sealing reagent (P188) was able to stabilize the membrane from mdx myocytes and normalize the $[Ca^{2+}]_I$ in these cells even after stretch, indicating an alternative Ca^{2+} leak pathway (67).

Signaling arising from Z-disks also share cross talk with Ca^{2+} signaling pathways. For instance, it was recently reported that Calsarcin1 [myozenin 2 (MYOZ2)], a signaling molecule located at the Z-disks, binds to the structural proteins such as α-actinin, γ -filamin, telethonin/T-cap, and the anchoring protein ZASP/Cypher/Oracle is also a calcineurin-binding protein (68-71). This protein seems to exert an inhibitory influence in Ca^{2+}-calmodulin-dependent signaling as indicated by the exaggerated left ventricular hypertrophy in response to chronic aortic coarctation in mice with cardiac-specific deletion of MYOZ2 (72).

An interaction between the titin domain located near Z-disk and obscurin suggests an additional role for titin in the SR organization (73). Obscurin interacts with ankyrin isoform 1.5 that might in turn mediate a contact with SR (74). These Z-disk region interactions suggest a general role for titin in positioning SR and T-tubule systems in close proximity to the I-band and perhaps ensuring that these systems move with the Z-disk, which may be important to their function and integrity. ANK 2.2, a member of ANK family that displays a similar ANK 1.5 obscurin binding site has been shown to link the SR to the sarcomere as well as to regulate ryanodine receptor distribution in the SR (75). Specifically in cardiac myocytes, a small region at the C-terminus of ANK 2.2 is involved in the ryanodine receptors localization (76). However, no direct evidence exists yet to confirm that ANK 1.5 connect the obscurin/titin complex to SR. Finally, T-cap also interacts with and may contribute to regulate MLP, which in turn is related to Ca^{2+} signaling (77).

There are also connections between the caveolae and the cystoskeletal proteins that are suspected to contribute to the assembly of signaling molecules in the caveolae as well as to determine a role for the caveolae in the mechanotransduction (78). Cardiac myocytes from caveolin-3 null mice (which lack caveolae) show histological abnormalities and T-tubule defects and develop cardiomyopathies (79).

6. MECHANICAL STRESS AND Ca^{2+} SIGNALING

Ca^{2+} signaling has been reported to play a role in regulating gene expression in response to mechanical stress

in cardiac myocytes (80). Several lines of evidence support a general model in which mechanical stimuli lead to the rise of intracellular Ca^{2+} activating signaling molecules that in turn leads to the engagement of pathways involved in the regulation of contractile activity and the transcriptional process. In this context, mechanical stress increases intracellular Ca^{2+} and the activity of Ca^{2+}-dependent effectors such as calcineurin and CaMKII (80, 81). Inhibitors of calcineurin and CaMKII attenuate the hypertrophy induced by mechanical stress (80, 82). As reviewed above, such signaling processes are expected to take place initially at discrete regions of T-tubules close to the costameres and Z-disks where the Ca^{2+} channels, transporters and signaling proteins are clustered.

Stretching single cardiac myocytes or multicellular myocardial preparations from slack length has been shown to cause a slow increase in the amplitude of the electrically stimulated Ca^{2+} transient and, in parallel, increase in the contractile force development and action potential duration (83-86). Studies performed in single cardiac myocytes provided some quantitative data of this process. Stretching the cells from 1.8 to 1.9 μm for 5 minutes leads to reversible increases of Ca^{2+} transient of ~10%, with apparently no change in the diastolic Ca^{2+}, supporting the idea that increased Ca^{2+} loading takes place during systole (83). Moreover, the slow increase in the Ca^{2+} transient has been indicated to be determined by enhanced Ca^{2+} entry rather than SR Ca^{2+} release (87). Increases in the transient of sarcomeric space Ca^{2+} induced by stretch increases cell contractility by interacting with troponin C and increasing the active cross-bridge between myosin to actin. In addition, several lines of evidence imply mechanisms intrinsic to the sarcomeres that results in increased sensitivity of the myofilaments to Ca^{2+} as a major factor that determines the changes in the contractile activity in response to mechanical loading (88). Actually, the sarcomeric intrinsic processes seem to be relatively more significant than the processes extrinsic to the sarcomere in the regulation of contractile activity of cardiac myocytes in response to stretch (89). However, the mechanisms by which active force generation become more sensitive to Ca^{2+} in overloaded myocytes remain unclear.

The mechanisms mediating the slow increases in the Ca^{2+} transient amplitude in response to stretch remain controversial. Although in the cardiac cell, the major Ca^{2+} influx pathway is the L-type Ca^{2+} current, the slow calcium entry does not seem to occur via this particular channel as it is not inhibited by Ca^{2+} channel blockers (87, 90). Instead, SACs have been implied as potential candidates to mediate the increase in intracellular Ca^{2+} and the delayed inotropic response to stretch, as indicated by the data from studies with SAC-pharmacological inhibitors such as streptomycin and Gd^{3+} (62, 91). In addition to directly conducting Ca^{2+} ions, SACs have been suspected to increase Ca^{2+} transient indirectly by conducting Na^{+} that then stimulates outward sodium/calcium exchange by NCX. Accordingly, the Na^{+}/H^{+} exchanger (NHE) inhibitor HOE 642 was demonstrated to attenuate the slow increase in Ca^{2+} transient in response to stretch in isolated papillary muscles and in single myocytes (92-95). Besides the pharmacological data, several lines of evidence further support the existence and the role of coupling between SACs, NHE and NCX in the rise of intracellular Ca^{2+} in response to stretch in cardiac myocytes. The NHE and NCX have been demonstrated to be concentrated and co-localized in the T-tubular portion of the sarcolemmal membrane (35, 96). Further, a steep $[Na^{+}]_I$ gradient exists between the subsarcolemmal space and bulk cytosol in the cardiac cell (97). The blockade of the Na^{+}/H^{+} exchanger both suppressed stretch-dependent enhanced calcineurin activity and hypertrophy (98).

In addition to changes in Ca^{2+} transient induced by stretch, it is equally plausible that mechanical forces induce the mobilization of more specialized pool of Ca^{2+}, which could activate local signaling systems. Stretch can increase the opening probability of the voltage-regulated L-type Ca^{2+} channel (87, 90). Ca^{2+} channel agonists or ionophores increase intracellular Ca^{2+} concentration and up-regulate the expression of hypertrophic gene markers (80). On the contrary, reduction of extracellular Ca^{2+} or the L-type Ca^{2+} channel blocker nifedipine suppressed stretch-dependent hypertrophy (80). Ca^{2+} influx through L-type Ca^{2+} channels may mediate adverse growth and remodeling of the heart. Overexpression of α_{1C} subunits in the hearts of transgenic mice led to increased L-type current density and a slowly developing, late-onset cardiac hypertrophy that eventually transitioned to heart failure, indicating that increased calcium influx could impact myocardial growth and remodeling (99). Recently, it was demonstrated that transgenic overexpression of the L-type Ca^{2+} channels in mice induces myocyte necrosis as a consequence of dysregulated Ca^{2+} handling and β-adrenergic receptor signaling, resulting in heart failure (100). Correspondingly, administration of L-Type Ca^{2+} channel or β-adrenergic receptor antagonists has been shown to be beneficial in a number of hypertrophy and failure models (100-103). However, none of these studies provided mechanistic data linking L-type current, intracellular signaling with mechanical stress.

Alternatively, activation of members Trp (transient receptor potential) family of channels by mechanical stress are also candidates to be involved in the modulation of Ca^{2+} entry induced by mechanical stress in cardiac myocytes. In recent studies performed in HEK293 and CHO cell lines, TrpC6, a member of the transient receptor potential channel expressed in many cell types, including the cardiac myocytes, was demonstrated to be sensitive to mechanical stimulus. A model suggests that stretch of the sarcolemma causes membrane thinning, inducing exposure and/or conformational alterations in TrpC6 channel resulting in its open state, which allows Ca^{2+} cellular influx in stretched cells (104). Therefore, TrpC6 channel may play a role in modulating the intracellular changes in concentration of Ca^{2+} induced by mechanicals stimulus. However, the importance of this mechanism in cardiac myocytes remains to be demonstrated. Interestingly, cardiac-specific overexpression of TrpC6 in transgenic mice has been shown to induce hypertrophy dependent on calcineurin-NFAT activation (105). Further evidence of the possible contribution of TrpC channels to the mediation of

hypertrophy growth in cardiac myocytes was provided by studies in which depletion of TrpC3 by siRNA was demonstrated to blockade the induction of hypertrophy genes in cardiac myocytes in response to hypertrophy agonists (106).

7. CONCLUSION

The recent years have seen a rapid increase in our understanding of signaling mechanisms activated by mechanical stress as well as those activated by Ca^{2+} in cardiac myocytes. Some of intermediate signaling molecules activated by mechanical stress or Ca^{2+} such as FAK, MLP, titin, calcineurin and CaMKII were identified and data are now available supporting their relative importance to the responses of cardiac myocytes to mechanical stress. However, we still lack a complete view of how mechanical forces are sensed and converted into biochemical or Ca^{2+} signals as well as how the various signaling mechanisms are integrated and can influence the pathophysiology of cardiac hypertrophy and failure.

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Key Words: Mechanical Stress, Signal Transduction, Heart, Hypertrophy, Review

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