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Linking Cardiac Mechanosensing at the Sarcomere M-Band, Nuclear Factor κB Signaling, and Cardiac Remodeling

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How the heart senses increased biomechanic stress and converts this "input signal" to generalized downstream cardiac hypertrophy signaling paradigms remains an enigmatic but intriguing question in modern cardiovascular biology. Only recently have signaling molecules that can couple biomechanical stress to common pathways of cardiac hypertrophy been uncovered. Yeast-2-hybrid screens have identified several binding partners of sarcomeric proteins. These concerted actions revealed that especially the sarcomere Z-disc harbors key components that affect the activity of several notable kinases and phosphatase, including mitogen-activated protein kinases, protein kinases A and C, and calcineurin. [1] Exemplary to this is the family of calsarcin proteins, which link the Z-disk protein α-actinin to calcineurin, a well-characterized Ca^{2+}-responsive signaling molecule controlling activity of the transcription factor NFAT and both required and sufficient for cardiac hypertrophy after pleiotropic stimuli (►Fig. 1). [2] However, interruption of the calcium overload typical for heart failure may not stop disease progression, and, therefore, Ca^{2+}-independent signaling cascades might serve as useful targets to interfere with left ventricular (LV) remodeling on pressure overload or ischemia. [3]

Likewise, the giant sarcomeric protein titin is the starting point of a signaling complex where the zinc-finger protein nbr1 targets the ubiquitin-associated p62/SQSTM1 to sarcomeres. In turn, p62 interacts with MuRF2, a muscle-specific RING-B-box E3 ligase and ligand of the transactivation domain of the serum response transcription factor. Nuclear translocation of MuRF2, provoked by mechanical inactivity, causes reduction of nuclear serum response transcription factor and repression of serum response transcription factor–mediated transcription (►Fig. 1). [4] Finally, cardiac mechanosensing might not be limited to the Z-disc only but can also derive from the M- and I-band regions, as well as the costamere, intercalated disks, and caveolae-like microdomains. [1]

The study by Li et al [5] published in this issue of *Hypertension* now adds an interesting new player to this emerging field in the form of myofibrillogenesis regulator-1 (MR-1). The authors identified MR-1 earlier as a binding partner of the M-band proteins myosin regulatory light chain, myomesin, and ß-enolase (►Fig. 1). In the current work, they describe the phenotype of transgenic mice overexpressing human MR-1 in the heart muscle. The study complements previous observations by the authors that MR-1 is upregulated in a rat model of pathological cardiac hypertrophy secondary to angiotensin II (Ang II) infusion or abdominal aortic banding. Conversely, small interfering RNA–mediated knockdown of MR-1 inhibited cardiomyocyte hypertrophy in culture. The current article not only elevates their observations to an in vivo context but also provides some molecular insight to the workings of MR-1 in cardiac pathogenesis.

MR-1 transgenic mice display no obvious baseline phenotype, which stimulated the authors to analyze the effect of MR-1 overexpression on Ang II–induced cardiac hypertrophy. Here, a rather high dose was chosen that not only leads to hypertrophy and severely elevated blood pressure but also to rapid decline of systolic LV function in control mice. Both changes, cardiac hypertrophy as determined by heart weight/body weight and LV remodeling resulting in severe LV dysfunction, were aggravated in MR-1–overexpressing mice. This observation was associated with an exaggerated increase in classical hypertrophy marker gene expression, inflammation, and fibrosis.

Mechanistically, the authors linked their observations to NF-κB signaling. MR-1 overexpression robustly increased NF-κB activity after Ang II stimulation as evidenced by DNA binding, p65 phosphorylation, IκBα phosphorylation and IκBα kinase activity. Likewise, adenoviral overexpression of MR-1 increased NF-κB activity after Ang II treatment of isolated cardiomyocytes. In association with the effect on hypertrophy, small interfering RNA- mediated MR-1 knockdown abolished NF-κB activity on Ang II treatment. In vitro, NF-κB activity was required downstream of MR-1 to evoke cardiomyocyte hypertrophy as adenoviral transfer of a mutated, nondegradable IκBα isoform abolished cardiomyocyte hypertrophy. Finally, the

authors also found increased levels of NF-κB regulated, proinflammatory cytokines membrane cofactor protein-1, interleukin-6, and tumor necrosis factor-α in association with increased fibrosis and collagen deposition in MR-1–overexpressing mice.

In summary, the authors propose a hierarchy of signaling events that places MR-1 at the sarcomere M-band at an integral point between cardiomoycte angiotensin receptor activation and NF-κB activation, which, in turn, drives cardiac hypertrophy and LV remodeling (►Fig. 1). Although the study has some limitations concerning the definition of hypertrophy (echocardiographic diastolic wall sizes and myofiber cross-sectional areas are missing), Ang II doses used (0.6 mg/kg per day leading to a blood pressure elevation of ≈40 mm Hg), and details on the MR-1–overexpressing mouse model, the findings are novel and interesting given the link between cardiac mechanosensing and specific Ca^{2+}-independent nuclear signaling pathways.

NF-κB activity has been associated with Ang II–induced hypertrophy and LV remodeling in several previous publications. In vivo, heart-restricted expression of a single copy of IκBαδN, a NF-κB superrepressor generating phenotypes similar to IκBα kinase knockouts when expressed globally, attenuates cardiac hypertrophy after Ang II and isoproterenol stimulation. [6] Upstream of NF-κB, Ang II was found to be a weak activator of DNA binding in adult rat cardiomyocytes; however, interleukin-6 cytokines released from cardiac fibroblasts on Ang II stimulation were found to be strong stimuli. [6] Furthermore, reactive oxygen species and the apoptosis signal-regulating kinase 1 have been implicated in G protein–coupled receptor-induced cardiac hypertrophy mediated through NF-κB. [7] Downstream, NF-κB activity regulates mRNA and protein levels of the gp130 receptor known to be important for cardiomyocyte survival signaling and hypertrophy probably through an indirect mechanism. [6] In addition, iex-1 was identified as an biomechanical strain-induced, NF-κB dependent, antihypertrophic protein expressed in cardiomyocytes. [8] Also, using a model of mechanical strain applied on isolated cardiomyocytes, Liang et al [9] identified the p38 mitogen-activated protein kinase/NF-κB axis to be required for B-type natriuretic peptide gene transcription.

Therapeutically, peroxidase proliferator-activated receptor-γ activators have been found to inhibit cardiomyocyte hypertrophy via suppression of mechanically induced NF-κB activation. [10] NF-κB inhibition has been found to improve LV remodeling on experimental infarct via downregulation of metalloproteinase-9 activity known to be controlled transcriptionally by NF-κB. [11] In summary, the AngII/MR-1/NF-κB axis now adds a new player to the sarcomere-linked signaling cascades controlling LV remodeling on stress. Data are now needed that demonstrate inhibition of these factors to not only affect cardiac hypertrophy but also to preserve LV function in the presence of chronic pressure overload or ischemia. This would confirm MR-1 and NF-κB to be part of the maladaptive cardiac hypertrophy signaling complex. Data from genetically engineered mice with deletion of MR-1 are eagerly awaited to confirm the findings presented in the current article.

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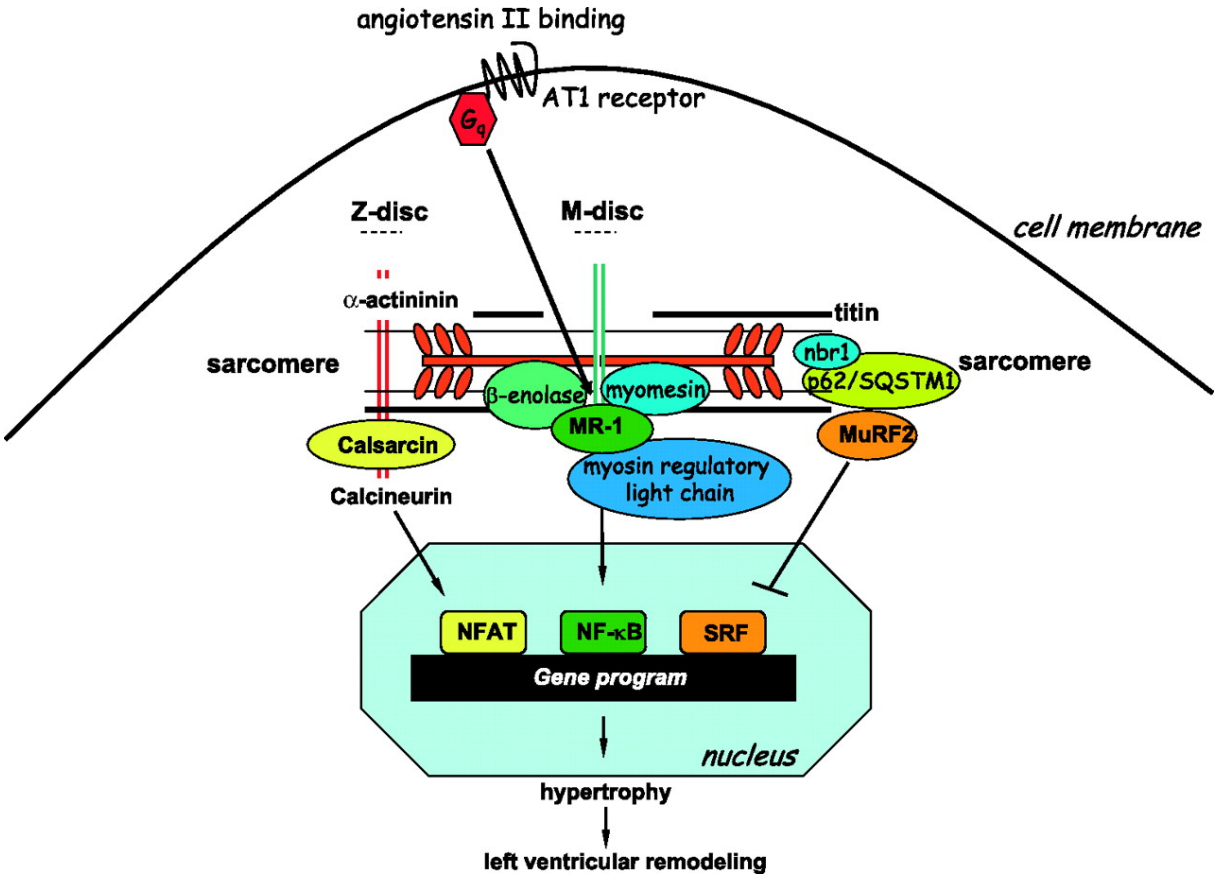

►Fig.1. Hypothetical signaling cascade linking Ang II signaling, cardiac mechanosensing at the sarcomere, and specific transcription factors in LV remodeling.