

## Multi-facets of Serum Response Factor in the Cardiac Pathophysiology

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### Summary

Heart is a vital organ that pumps blood to all body parts of an organism through synchronous contraction and relaxation movements of the cardiac muscle. Homeostasis of cardiac muscle is thus necessary for normal heart functioning. Fine tuning of the cardiac muscle is maintained by numerous signal transduction pathways which are not only responsible for physiological functions, but pathological lesions as well. Many intrinsic or extrinsic stimuli like physical stress, pressure overload, hypertension, etc. disturbs cardiac homeostasis and affects signal transduction pathways causing disease phenotype such as hypertrophy, cardiomyopathy, and consequent heart failure. The most unique characteristic of cardiomyocytes is that they are terminally differentiated and do not grow in number postnatally, they only grow in size by lateral/longitudinal hypertrophy. Hypertrophy is also induced in cardiomyocytes to overcome acute wall tension caused by various biochemical stresses. At molecular level, several signalling pathways and interacting networks have been implicated with the heart's molecular response to physiological and/or pathological biomechanical stress, reviewed in detail elsewhere [1-4]. Calcineurin, a Ca<sup>2+</sup>-calmodulin activation dependent serine-threonine phosphatase is one of the key signaling molecules strongly linked to cardiac hypertrophy [5-8]. Its prohypertrophic effects are well established through series of *in vitro* and *in vivo* studies and is highly correlated with human patients of cardiac hypertrophy and cardiomyopathy [6,9]. Moreover, Calcineurin signaling is found to be interconnected with many other important hypertrophic pathways, such as those controlled by glycogen synthase kinase (GSK) 3 $\beta$  and mitogen-activated protein (MAP) kinase signaling [3,10]. Interestingly, Rho family of small GTPase proteins, consisting of Rho, Rac, and Cdc42 subfamilies regulate the sarcomere organization in cardiomyocytes, one of the hallmarks of hypertrophy [11]. These GTPase effectors are also upstream of a very important cardiac signaling molecule, serum response factor (SRF) [12,13].

SRF is a highly conserved, ubiquitously expressed, and multifunctional founding member of the MADS (MCM1, Agamous, Deficiens, and SRF) box family of transcription factors, that has long been considered central to several regulatory complexes in muscle and non-muscle cells [14]. SRF regulates the expression of many muscle-specific and mitogen-responsive genes including some of the hypertrophy markers such as atrial/brain natriuretic

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peptides (ANF/BNP), Myosin heavy chains and  $\alpha$ -skeletal/cardiac actin, through binding to single or multiple consensus CAR<sub>G</sub> box (CC[A/T]2A[A/T]3GG) element in their promoter or enhancer sequences [15]. SRF in addition to affecting its target gene expression, also recruits different transcription factors in the heart, such as, cardiac NK2 Homeobox 5 (Nkx2.5), Transcriptional enhancer factor 1 (TEF-1), cardiac GATA family factors, and cofactors like myocardin, and of myocardin-related transcription factors [16-20]. SRF is therefore at the juncture of multiple signaling pathways that binds to serum response element in the promoter region of target genes and regulates the activity of many immediate-early genes, thereby participating in cell cycle regulation, apoptosis, cell growth, and cell differentiation in other cell types, and cell growth and homeostasis in cardiomyocytes.

Further insights into cardiac role of SRF were deduced from loss- and gain-of-function approaches *in vivo* in mice. Classical global deletion of *Srf* leads to a very early embryonic lethality in mice,

with a prominent defect in mesoderm formation, which hampered further evaluation of cardiac role of SRF [21]. To overcome this problem, Parlakian et al. has generated a mutant mouse line with targeted deletion of SRF in the heart [22]. They found that mice with early depleted cardiac SRF expression display severe cardiac defects, impaired expression of critical cardiac transcription factors such as *Nkx2.5/GATA4/myocardin*, and die between embryonic day 10.5 (E10.5) and E13.5 of development [22]. Similarly, Miano et al., generated mice where SRF was knocked out in >80% of cardiomyocytes and >50% of vascular smooth muscle cells using SM22alpha-Cre-mediated excision of promoter and first exon of SRF. They also noticed both cardiac and vascular defects such as highly disorganized sarcomere, defective actin/intermediate filament bundles, and cardiac looping resulting embryonic death at E11.5. On the other hand, disruption of SRF in adult heart using a heart-specific Tamoxifen- inducible Cre recombinase led to progressive dilated cardiomyopathy and heart failure due to decreased expression of proteins involved in force generation and transmission, low levels of polymerized actin, and changes in cytoarchitecture without hypertrophic compensation [23]. Moreover, the symptoms observed in SRF-deficient mice at adolescence resemble morphological and clinical features of acquired dilated cardiomyopathy in humans. Furthermore, cardiac-sustained overexpression of SRF in transgenic mice is sufficient to develop cardiac hypertrophy and cardiomyopathy [24], whereas, overexpression of dominant-negative form of SRF

in mice causes dilated cardiomyopathy [25]. These findings also have physiological and pathological relevance since the basal expression of SRF protein is found to be increased in old compared to young adult rat hearts [26], and an increased expression of an alternatively spliced dominant-negative isoform of SRF was observed in failing human hearts [27]. Taken together, findings from transgenic *in vivo* mouse models further strengthens the view that SRF is one of the downstream effectors of the signaling pathways involved in the induction of cardiac hypertrophy.

SRF has recently been implicated in the regulation and biogenesis of certain microRNAs [28]. miR-1, miR-21 and miR-133, all of which have established cardiac role, were found to be under direct regulation of SRF, adding not only another layer of complexity, but also provide an opportunity to explore for the therapeutic potential of SRF [28]. All these findings together undeniably demonstrate that SRF is crucial for cardiomyogenesis, adult cardiac function and integrity, and acts as a global regulator of multiple developmental genes and signaling cascades. SRF thus pose a strong therapeutic target for the treatment of cardiac diseases like cardiac hypertrophy, dilated cardiomyopathy and progressive heart failure. To revisit the existing knowledge, and the identification and characterization of yet unknown activators, inhibitors, and upstream and downstream effectors of this cardinal cardiac signaling molecule will therefore increase the possibilities of finding suitable drug molecule against the chronic cardiac diseases.

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