A new stone for a new path, from “physiology to the bedside”

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Left ventricular hypertrophy (LVH) is prevalent in clinical practice; it is associated with increased risk of heart failure, diastolic dysfunction, arrhythmias, and sudden cardiac death. Typical LVH is defined as the thickening of interventricular wall and/or septum in non-invasive imaging [3, 5]. Microscopically, the sizes of cardiomyocytes of LVH region are enlarged, accompanied by the augmentation of protein synthesis, sarcomeric structural disarray, and apoptosis [3]. Molecular mechanisms of the initiation and progression of LVH downstream of pathological stimuli have been of intensive research for over half a century. Nevertheless, current pharmacological therapy resembles that for heart failure, including β adrenoreceptor -blockers, Ca antagonists, diuretics, angiotensin-converting enzyme (ACE) inhibitors, antioxidants, metabolic therapies, β_3 AR-agonist, mitochondrial ROS degenerating compounds, or agents regulate protein homeostasis [5, 11]. It is timely to develop a new strategy for specific and effective treatment of LVH.

The etiology of LVH is diverse, with the majority caused by sarcomeric mutations (account for ~60% of LVH in humans), but vasculopathy, fibrosis, hypertension, ischemia, inflammation, etc. are also substantial precursors [3, 6]. Upon stimulation, an array of cellular responses are triggered, including myofilament Ca^{2+} sensitization, metabolic disorder, and redox imbalance, which lead to irreversible remodeling of cardiomyocytes and ultimately LVH (the vicious cycle) [11].

General consensus of the key cardiac hypertrophy signaling pathways is Ca-calculinurin-nuclear factor of activated T cell (NFAT), MAP kinase (MAPK), or mTOR-dependent protein transcription and expression [7, 8], based on studies using myocardial biopsies from LVH patients or cultured adult and neonatal cardiomyocytes; animal models, such as transgenic mice, surgically (transverse aortic constriction) or chemically (neurohormonal peptide induced hypertension)-induced LVH, or spontaneous hypertensive rats [2, 7, 8, 12, 13]. Critical upstream regulators involve phosphoinositide-specific phospholipase C activation, phosphoinositol 4,5-bisphosphate hydrolysis, and inositol 1,4,5 trisphosphate (IP_3) and diacylglycerol (DAG) production [12]. IP_3 and DAG are well known to elevate $[\text{Ca}^{2+}]_i$, through ryanodine receptor Ca release and Ca influx via TRPC channels [9, 10] and L-type Ca channels [4]. $[\text{Ca}^{2+}]_i$, in turn, activates serine/threonine phosphatase calcineurin, which dephosphorylates NFAT leads to its nuclear translocation to initiate the transcription and expression of proteins [7, 8].

In this issue, Deisl et al. from Donald W. Hilgemann's laboratory iterated the important hypertrophic signaling using human embryonic stem cell-derived and spontaneously beating cardiomyocytes (hESC) [1]. Cultured for 2–4 months after the differentiation, they have presented clear evidence that G protein-coupled, potent hypertrophic stimulators (endothelin-1 and angiotensin II) or fatty acid mixture (palmitic, myristic and palmitoleic acids) induced hypertrophy (assessed by greater α -actinin and β -myosin heavy chain protein expressions) mediated by intracellular DAG and Ca-dependent signaling. DAG lipase inhibitor, DO34 (which increased cellular DAG level), increased $[\text{Ca}^{2+}]_i$. In addition, cardiac glycoside, ouabain, increased DAG, indicating positive regulatory loop between DAG and $[\text{Ca}^{2+}]_i$, and both mechanisms contributed equally to hypertrophic phenotype in hESC-derived cardiomyocytes. The study provided evidence to prove that hESC-derived cardiomyocytes can be a useful tool to investigate upstream and downstream mechanisms of human cardiac hypertrophic progression long term (over months). It should be noted that hESC-derived cardiomyocytes possess the advantages of complementing diverse genetic and pharmacological

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modifications including those of inflammation, to underpin key mechanisms from comprehensive hypertrophic signaling paradigm. Combine with genome, transcriptome, and proteome at the onset, during and after the development of hypertrophy, true “Alliance for Cell Signaling” is expected to be revealed for better incorporating individual mechanisms into the hypertrophic scenario in patients.

In conclusion, employing stem cells in preclinical and clinical investigations are of great potential for the clinical applications to tackle human cardiovascular diseases. hESC-derived LVH research will pave the new stone to the path for early prevention and treatment of myocardial hypertrophy and reduce LVH-based mortality.

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