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Molecular distinction between physiological and pathological cardiac hypertrophy: Experimental findings and therapeutic strategies

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ABSTRACT

Cardiac hypertrophy can be defined as an increase in heart mass. Pathological cardiac hypertrophy (heart growth that occurs in settings of disease, e.g. hypertension) is a key risk factor for heart failure. Pathological hypertrophy is associated with increased interstitial fibrosis, cell death and cardiac dysfunction. In contrast, physiological cardiac hypertrophy (heart growth that occurs in response to chronic exercise training, i.e. the 'athlete's heart') is reversible and is characterized by normal cardiac morphology (i.e. no fibrosis or apoptosis) and normal or enhanced cardiac function. Given that there are clear functional, structural, metabolic and molecular differences between pathological and physiological hypertrophy, a key question in cardiovascular medicine is whether mechanisms responsible for enhancing function of the athlete's heart can be exploited to benefit patients with pathological hypertrophy and heart failure. This review summarizes key experimental findings that have contributed to our understanding of pathological and physiological heart growth. In particular, we focus on signaling pathways that play a causal role in the development of pathological and physiological hypertrophy. We discuss molecular mechanisms associated with features of cardiac hypertrophy, including protein synthesis, sarcomeric organization, fibrosis, cell death and energy metabolism and provide a summary of profiling studies that have examined genes, microRNAs and proteins that are differentially expressed in models of pathological and physiological hypertrophy. How gender and sex hormones affect cardiac hypertrophy is also discussed. Finally, we explore how knowledge of molecular mechanisms underlying pathological and physiological hypertrophy may influence therapeutic strategies for the treatment of cardiovascular disease and heart failure.

Abbreviations: 4E-BP1, 4E binding protein 1; ACE, Angiotensin converting enzyme; ACEI, Angiotensin converting enzyme inhibitors; Adr, adrenaline; Ang II, Angiotensin II; ANP, Atrial natriuretic peptide; ARB, Angiotensin receptor blockers; ARK, Adrenergic receptor kinase; ARs, Adrenergic receptors; AT_1, Angiotensin type 1 receptor; BNP, B-type natriuretic peptide; ca, constitutively active; CaM, calmodulin; CaMK, calcium/calmodulin-dependent protein kinases; *c-fos*, *c-fos* oncogene; *c-jun*, *c-jun* oncogene; *c-myc*, *c-myc* oncogene; Cn/CN, calcineurin; CoA, coenzyme A; CREB, cAMP response element-binding protein; CT-1, cardiotrophin 1; cTNT, cardiac troponin T; DAG, diacylglycerol; DCM, dilated cardiomyopathy; dn, dominant negative; ECM, extracellular matrix; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; eIF2, eukaryotic initiation factor 2; eIF4E, eukaryotic initiation factor 4E; ER, estrogen receptor; ERK, extracellular signal-regulated kinases; ET_A, endothelin type A receptor; ET-I, endothelin 1; FAK, focal adhesion kinase; GATA, GATA protein binding; Gp, guanine nucleotide binding proteins; GPCR, G protein-coupled receptor; Grb2, growth factor receptor bound protein 2; GSK3, glycogen synthase kinase 3; HDAC, histone deacetylase; HIF, hypoxia-inducible factor; HSF1, heat shock transcription factor 1; Hsp, heat shock protein; HW/BW, heart weight/body weight ratio; IGF1, insulin-like growth factor 1; IGF1R, insulin-like growth factor 1 receptor; IP_3, inositol 1,4,5-trisphosphate; JAK, Janus kinase; JNK, *c-Jun* amino-terminal kinase; JVS, juvenile visceral steatosis; KO, knockout; LIF, leukemia inhibitory factor; LVPW, left ventricular posterior wall; MAPK, mitogen activated protein kinase; MCAD, medium chain acyl coenzyme A dehydrogenase; MCIP, mitogen-enriched calcineurin-interacting protein; mCPT-1, muscle-type carnitine palmitoyltransferase 1; MEF2, myocyte enhancer factor 2; MEK, mitogen activated protein kinase kinase; MEKK, mitogen activated protein kinase kinase kinase; MHC, myosin heavy chain; miRNAs, microRNAs; MLC, myosin light chain; MLCK, myosin light chain kinase; mTOR, mammalian target of rapamycin; Nab1, NGF1A-binding protein; NADPH, nicotinamide adenine dinucleotide phosphate; NE, noradrenaline, norepinephrine; NFAT, nuclear factor of activated T cells; Ntg, non-transgenic; PDE, phosphodiesterase; PE, phenylephrine; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PKC, protein kinase C; PKD, protein kinase D; PLB, phospholamban; PLC, phospholipase C; PPAR, peroxisome proliferation-activated receptors; pS6, phosphorylation of 40 S ribosomal S6 protein; Rab, member of RAS oncogene family; Raf1, member of RAS oncogene family; Ran, member of RAS oncogene family; Ras, Ras oncogene; Rho, rhodopsin; ROS, reactive oxygen species; RTK, receptor tyrosine kinase; S6K, ribosomal S6 kinase; SERCA, sarcoplasmic reticulum Ca^{2+}-ATPase; Src, *Rous sarcoma* oncogene; STAT, signal transducer and activator of transcription; TAK, TGF-β activated kinase; Tg, transgenic; TGF, transforming growth factor; TNF, tumor necrosis factor; TR, thyroid hormone receptor; Ub, ubiquitin; WT, wildtype.

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Contents

1. Cardiac hypertrophy

1.1. Introduction and overview

Cardiac hypertrophy can broadly be defined as an increase in heart mass. Growth of the postnatal heart is closely matched to its functional load (Zak, 1984). In response to an increase in load (e.g. pressure overload in a setting of hypertension), the heart must work harder than under normal conditions. To counterbalance the chronic increase in wall stress the muscle cells within the heart enlarge leading to an increase in size and mass (Cooper, 1987; Sugden & Clerk, 1998; Hunter & Chien, 1999). The increase in heart mass is largely due to an increase in ventricular weight. In the subsequent sections we have described cardiac hypertrophy at the cellular level, different types of cardiac hypertrophy (pathological and physiological), the molecular mechanisms responsible for different forms of cardiac hypertrophy, gender differences, and possible treatment strategies based on the distinct molecular mechanisms associated with physiological and pathological cardiac hypertrophy.

1.2. Cardiac hypertrophy at the cellular level

The heart is composed of cardiac myocytes (muscle cells), non-myocytes (e.g. fibroblasts, endothelial cells, mast cells, vascular smooth muscle cells), and the surrounding extracellular matrix (Nag, 1980; Zak, 1984). Ventricular cardiac myocytes make up only one-third of the total

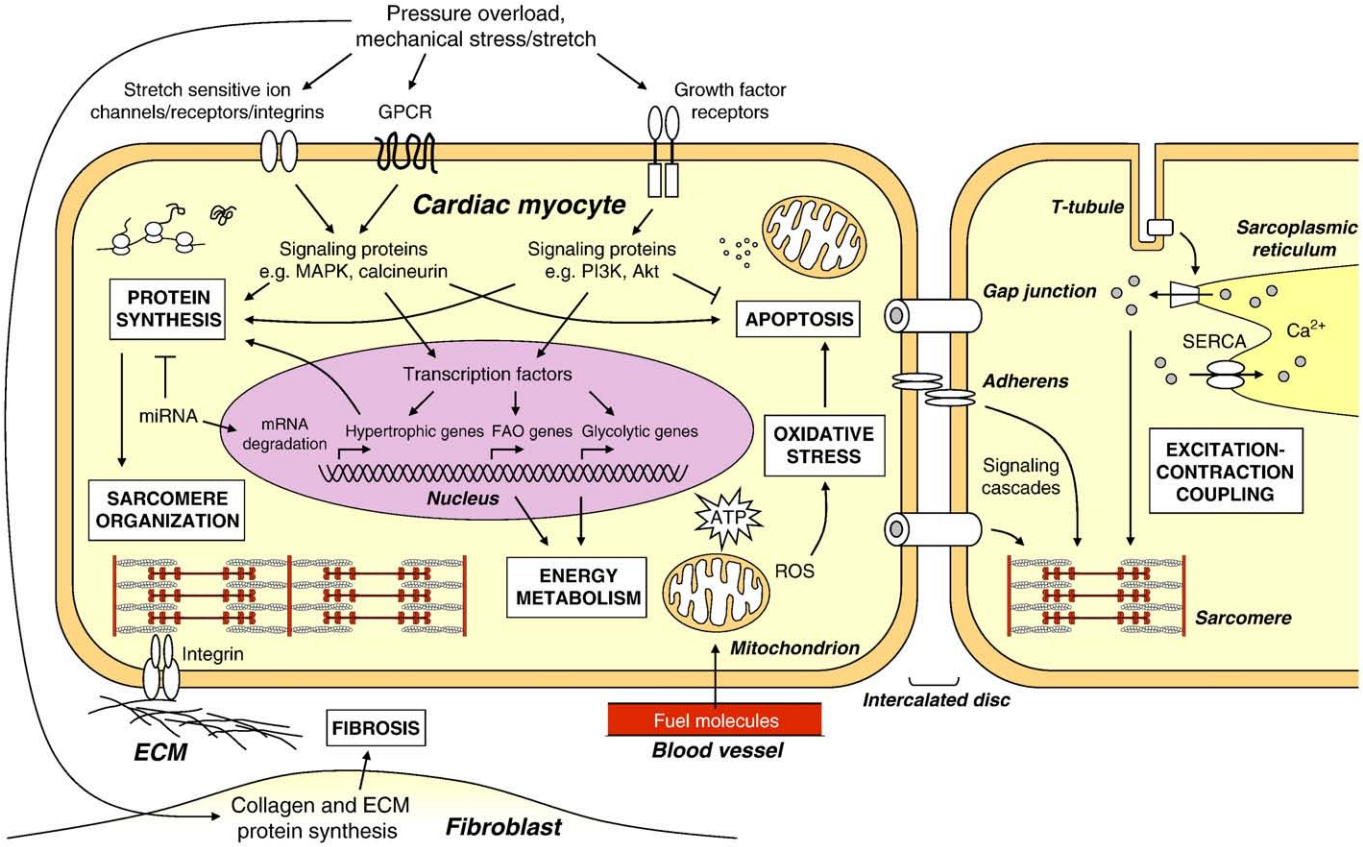

Fig. 1. Cellular processes involved in the development of cardiac hypertrophy. ECM: extracellular matrix, FAO: fatty acid oxidation, GPCR: G protein-coupled receptor, MAPK: mitogen-activated protein kinase, PI3K: phosphoinositide 3-kinase, ROS: reactive oxygen species, SERCA: sarcoplasmic reticulum Ca^{2+} ATPase.