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Review article

Redox regulation of cardiac hypertrophy

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ABSTRACT

It is increasingly evident that redox-dependent modifications in cellular proteins and signaling pathways (or redox signaling) play important roles in many aspects of cardiac hypertrophy. Indeed, these redox modifications may be intricately linked with the process of hypertrophy wherein there is not only a significant increase in myocardial O_2 consumption but also important alterations in metabolic processes and in the local generation of O_2-derived reactive species (ROS) that modulate and/or amplify cell signaling pathways. This article reviews our current knowledge of redox signaling pathways and their roles in cardiac hypertrophy. This article is part of a Special Issue entitled 'Redox Signalling in Heart'.

Contents

Abbreviations: AKAPs, A-kinase anchoring proteins; AKT, protein kinase b; Ang-II, angiotensin II; ASK1, apoptosis signal-regulating kinase 1; BH4, tetrahydrobiopterin; CaMKII, Ca/calmodulin-dependent kinase II; cGMP, cyclic guanosine monophosphate; CHF, chronic heart failure; CTGF, connective tissue growth factor; DCM, dilated cardiomyopathy; ECC, excitation–contraction coupling; ECM, extracellular matrix; ETC, electron transport chain; ER, endoplasmic reticulum; ERK1/2, extracellular signal-regulated kinase 1/2; Ero1, endoplasmic reticulum oxidase 1; GATA4, transcription factor GATA-4; C/EBPβ, transcription factor C/EBPβ; GPCR, G-protein coupled receptor; GSH, reduced glutathione; HADC, histone deacetylase; HIF, hypoxia-inducible factor; HNO, nitroxyl; H_2O_2, hydrogen peroxide; IGF, insulin-like growth factor; MI, myocardial infarction; MMP2, matrix metalloproteinase-2; LOX, lysyl oxidase; LV, left ventricle; MAO, monoamine oxidase; MEF2, myocyte enhancer factor-2; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; NOS, NO synthase; NOX, NAPDH oxidase; Nrf2, nuclear factor erythroid-2 related factor 2; O_2, molecular oxygen; O_2^-, superoxide; $ONOO^-$, peroxynitrite; p38MAPK, mitogen-activated protein kinase; PDI, protein disulfide isomerase; PGC1 , peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PHD, prolyl oxidase; PKA, cAMP-dependent protein kinase A; PKG, cGMP-dependent protein kinase G; PI3Kα, phosphatidylinositol 3 kinase alpha; RAAS, renin–angiotensin–aldosterone system; RNS, reactive nitrogen species; ROS, reactive oxygen species; RyR2, Ca release channels of the SR; SERCA2a, SR Ca2 + ATPase; SR, sarcoplasmic reticulum; SRF, serum response factor; SOD, superoxide dismutase; TGF , transforming growth factor ; TRX, thioredoxin; VEGF, vascular endothelial growth factor; XO, xanthine oxidase.

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1. Introduction

Cardiac hypertrophy represents an increase in cardiac muscle mass in response to a chronic increase in cardiac workload. It may be associated, at least initially, with an enhanced contractile function of the heart but chronic increases in workload due to disease stress generally result in a progressive decline in cardiac performance and ultimately the development of chronic heart failure (CHF). Such pathological hypertrophy usually occurs in response to chronically increased afterload or "pressure overload" (e.g. due to hypertension), increased preload or "volume overload" (e.g. due to valvular regurgitation), or following myocardial infarction (MI). In addition, pathological hypertrophy may also arise in diabetes and with genetic abnormalities of myocardial structure or function [1]. In contrast, reversible physiological hypertrophy with well compensated contractile function is seen in athletes or healthy pregnancy [2].

The development of cardiac hypertrophy involves a complex remodeling of cardiomyocyte structure and function as well as remodeling of the non-myocyte compartment (i.e. the vasculature and the extracellular matrix [ECM]). For instance, the maintenance of an appropriate capillary density and blood supply to match the increase in muscle mass is crucial for an adaptive hypertrophic response, whereas a mismatch promotes decompensation [3]. Maladaptive cardiac hypertrophy is accompanied by disproportionate interstitial fibrosis, energy deficit, cardiomyocyte death, vascular dysfunction and chamber dilatation [4].

It is increasingly evident that redox-dependent modifications in cellular proteins and signaling pathways (or redox signaling) play important roles in many aspects of cardiac hypertrophy [5]. Indeed, these redox modifications may be intricately linked with the process of hypertrophy wherein there is not only a significant increase in myocardial O_2 consumption but also important alterations in metabolic processes and in the local generation of O_2-derived reactive species (ROS) that modulate and/or amplify cell signaling pathways. This article reviews our current knowledge of redox signaling pathways and their roles in cardiac hypertrophy.

2. General considerations with respect to redox signaling in cardiac hypertrophy

At the cellular level, O_2 specifically undergoes one electron reduction to O_2^- through the action of several oxidases, either as their primary function or as a byproduct of some other reaction. These oxidases include NAPDH oxidases (NOXs), xanthine oxidase (XO), monoamine oxidase (MAO), and uncoupled NO synthases (NOS) (Fig. 1 and below). O_2^- is also produced by mitochondrial complexes I and II under certain circumstances. The O_2^- can become further dismutated to H_2O_2 via superoxide dismutases (SOD). Moreover, O_2 is used by NOS to produce nitric oxide (NO), a reactive nitrogen species (RNS) that may be the precursor of other reactive species (e.g. $ONOO^-$). The complex interplay and specific effect of these reactive species is greatly influenced by the amount

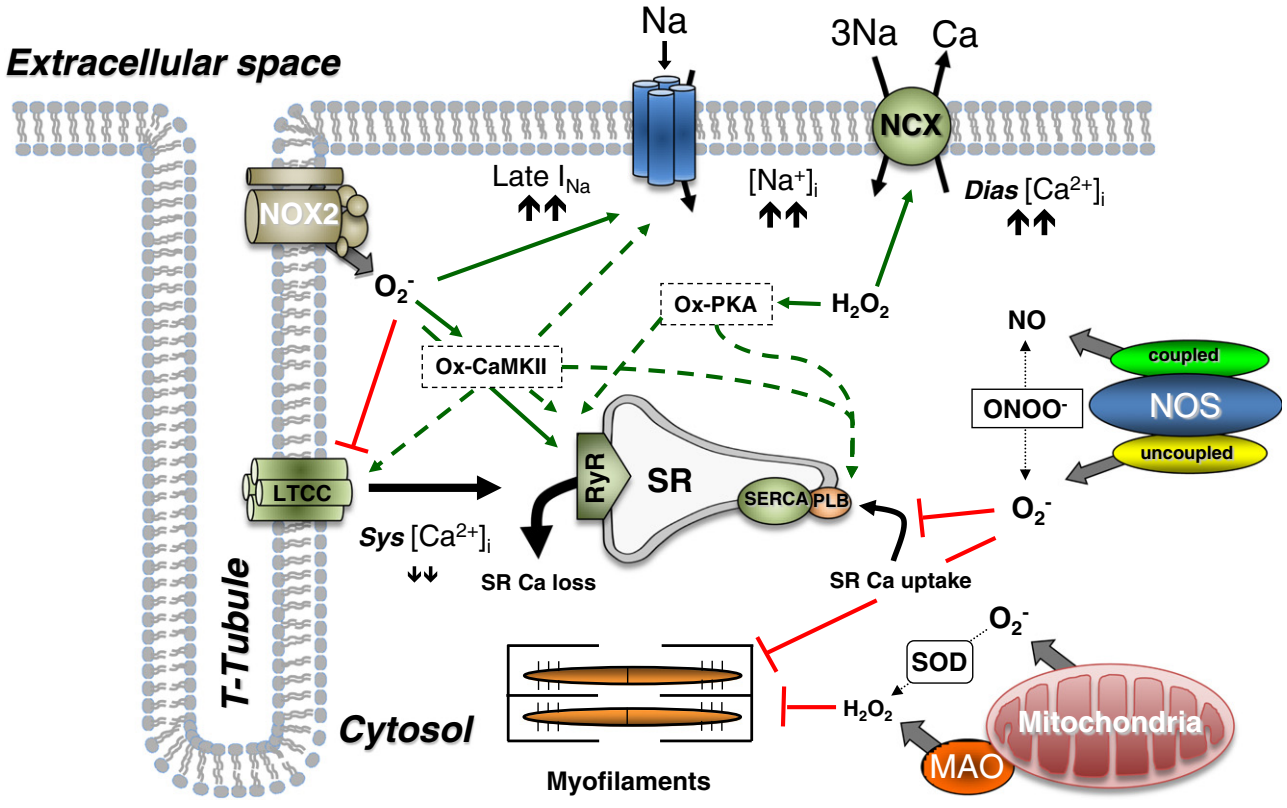

Fig. 1. Important intracellular ROS sources and selected targets involved in excitation-contraction coupling in the hypertrophied cardiac myocyte. ROS may have direct actions or indirect actions through modification of various kinases, resulting in an impairment of excitation–contraction coupling, i.e. a decrease of systolic (sys) Ca fluxes in the face of Na-dependent diastolic (dias) Ca overload. Solid green lines indicate activation, solid red lines inhibition; dashed lines indicate indirect effects via protein kinases. O_2^-, superoxide; H_2O_2, hydrogen peroxide.

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