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Role of copper in regression of cardiac hypertrophy

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ABSTRACT

Pressure overload causes an accumulation of homocysteine in the heart, which is accompanied by copper depletion through the formation of copper–homocysteine complexes and the excretion of the complexes. Copper supplementation recovers cytochrome c oxidase (CCO) activity and promotes myocardial angiogenesis, along with the regression of cardiac hypertrophy and the recovery of cardiac contractile function. Increased copper availability is responsible for the recovery of CCO activity. Copper promoted expression of angiogenesis factors including vascular endothelial growth factor (VEGF) in endothelial cells is responsible for angiogenesis. VEGF receptor-2 (VEGFR-2) is critical for hypertrophic growth of cardiomyocytes and VEGFR-1 is essential for the regression of cardiomyocyte hypertrophy. Copper, through promoting VEGF production and suppressing VEGFR-2, switches the VEGF signaling pathway from VEGFR-2-dependent to VEGFR-1-dependent, leading to the regression of cardiomyocyte hypertrophy. Copper is also required for hypoxia-inducible factor-1 (HIF-1) transcriptional activity, acting on the interaction between HIF-1 and the hypoxia responsible element and the formation of HIF-1 transcriptional complex by inhibiting the factor inhibiting HIF-1. Therefore, therapeutic targets for copper supplementation-induced regression of cardiac hypertrophy include: (1) the recovery of copper availability for CCO and other critical cellular events; (2) the activation of HIF-1 transcriptional complex leading to the promotion of angiogenesis in the endothelial cells by VEGF and other factors; (3) the activation of VEGFR-1-dependent regression signaling pathway in the cardiomyocytes; and (4) the inhibition of VEGFR-2 through post-translational regulation in the hypertrophic cardiomyocytes. Future studies should focus on target-specific delivery of copper for the development of clinical application.

Contents

Abbreviations: ANG-1, angiopoietin-1; ANG-2, angiopoietin-2; ANP, atrial natriuretic peptide; ATOX1, antioxidant 1; ATP, adenosine triphosphate; BNP, B-type natriuretic peptide; BNIP3, BCL2/adenovirus E1B 19 kDa protein-interacting protein 3; CCO, cytochrome c oxidase; COX-I, subunit I of cytochrome c oxidase; COX-II, subunit II of cytochrome c oxidase; COX11, cytochrome c oxidase assembly homolog 11; COX17, cytochrome c oxidase assembly homolog 17; CTR1, copper transporter 1; CTR3, copper transporter 3; CCS, copper chaperone for Cu–Zn superoxide dismutase; CuD, Cu deficiency; CuR, Cu repletion; ECs, endothelial cells; ECM, extracellular matrix; eNOS, endothelial nitric oxide synthase; FGF-1, fibroblast growth factor-1; FOXO, forkhead box protein; FIH-1, factor inhibiting HIF-1; GSK3β, glycogen synthase kinase 3 beta; Hcy, homocysteine; HIF-1, hypoxia-inducible factor-1; HIF-1α, hypoxia-inducible factor-1α; HIF-1β, hypoxia-inducible factor-1β; HRE, hypoxia response element; HUVECs, human umbilical vein endothelial cells; HMG-CoA, 3-hydroxy-3-methyglutaryl-coenzyme A; IGF-1, insulin-like growth factor-1; IGF-2, insulin-like growth factor-2; IM, inner mitochondrial membrane; IMS, intermembrane space of mitochondria; LVADs, left ventricular assist devices; MMPs, matrix metalloproteinases; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-κB; OM, outer mitochondrial membrane; OxPhos, oxidative phosphorylation; PDE-5A, phosphodiesterase-5A; PDK-1, phosphoinositide-dependent kinase-1; PE, phenylephrine; PHDs, prolyl hydroxylases; PKG-1, 3′,5′-cyclic monophosphate (cGMP)-dependent protein kinase-1; PLCγ, phosphoinositide phospholipase C gamma; pVHL, von Hippel–Lindau protein; RGS2, the regulator of G-protein signaling 2; ROS, reactive oxygen species; SCO1, cytochrome oxidase-deficient homolog 1; SCO2, cytochrome oxidase-deficient homolog 2; TEPA, tetraethylenepentamine; TRPC, transient receptor potential canonical; TM, tetrathiomolybdate; VASP, vasodilator stimulated phosphoprotein; VEGF, Vascular endothelial growth factor; VEGFR-1, VEGF receptor-1 (Flt-1, FMS-like tyrosine kinase-1); VEGFR-2, VEGF receptor-2 (KDR, kinase insert domain receptor); β-MHC, β-myosin heavy chain

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1. Introduction

Regression of pathological cardiac hypertrophy had been a debatable topic in cardiovascular research (Hou & Kang, 2012). The traditional view of pathological cardiac hypertrophy was that it was irreversible, but this view was challenged by a series of clinical observations and experimental studies that showed the reversibility of the pathological cardiac hypertrophy (Hou & Kang, 2012). The clinically relevant question is how to develop practical approaches to reverse pathological cardiac hypertrophy in patients?

Copper (Cu) supplementation can reverse pathological cardiac hypertrophy induced by dietary Cu deficiency in rats, which was observed in 1967 (Dallman, 1967). However, because the cardiac hypertrophy was induced by dietary Cu deficiency, the significance of the observation was not fully appreciated, although it was the first report to show that pathological cardiac hypertrophy was reversible. It was until 2007 that the role of Cu in the regression of pathological cardiac hypertrophy was extensively demonstrated in a study of cardiac hypertrophy induced by ascending aortic constriction in mice (Jiang et al., 2007). In that study, mice were fed Cu adequate diet (6 mg Cu/kg diet) and subjected to ascending aortic constriction for 4 weeks, developing pathological cardiac hypertrophy evidenced by the enlarged heart accompanied by defected contractile function and cardiomyopathy. Dietary supplementation of Cu (20 mg Cu/kg diet) to the mice with the established pathological cardiac hypertrophy for 4 weeks resulted in reversal of the cardiac hypertrophy and complete recovery of cardiac contractile function. This effect of Cu supplementation was further confirmed in studies using primary cultures of neonatal cardiomyocytes (Zhou et al., 2008, 2009; Zuo et al., 2010; Sun et al., 2014; Wang et al., 2014). How does Cu supplementation cause this regression?

Cu is required for the function of cytochrome c oxidase (CCO), the last complex in the mitochondrial respiratory chain and responsible for the transfer of electrons from cytochrome c to oxygen. Mitochondrial defects are observed in pathological cardiac hypertrophy, including respiratory chain oxidative phosphorylation (OxPhos) abnormalities and adenosine triphosphate (ATP) deficiencies (Marin-Garcia et al., 1995, 1996, 2001). The depression of CCO activity is highly responsible for the mitochondrial defect (Quigley et al., 2000), which is the result of Cu depression in the heart. Cu supplementation replenishes Cu availability and restores CCO activity in the heart subjected to sustained pressure overload along with the reversal of cardiac hypertrophy (Jiang et al., 2007). Thus, Cu supplementation-induced recovery of CCO activity plays a critical role in the regression of pathological cardiac hypertrophy.

The involvement of Cu in angiogenesis has been known for more than 30 years (McAuslan & Gole, 1980; Ziche et al., 1982; Augustin et al., 2009), but only recently is it realized that angiogenesis is critical for the reversal of pathological cardiac hypertrophy (Elsherif et al., 2004b; Yang et al., 2007). Therefore, understanding the role of Cu in angiogenesis is critical for the understanding of Cu regression of cardiac hypertrophy. This effect is related to the role of Cu in the biological function of endothelial cells, including their proliferation, migration, tube formation, and vessel maturation. The regulation of all of these aspects requires the participation of Cu.

Cu also directly acts on hypertrophic cardiomyocytes to activate the regression pathways besides its action on endothelial cells, leading to a series of reactions for the promotion of angiogenesis. Cu effect on the hypertrophic cardiomyocytes is fulfilled by inhibiting the VEGF receptor-2 signaling pathway, thereby making the VEGF receptor-1 pathway dominant leading to activation of the regression pathways. These novel understandings make a further insight into the mechanism for the regression of pathological cardiac hypertrophy, and define several targets for the development of therapeutic approaches for clinical application.

The molecular understanding for the multiple actions of Cu in the regression of pathological cardiac hypertrophy comes from the studies of Cu requirement for the transcriptional activity of hypoxia-inducible factor-1 (HIF-1) (Feng et al., 2009). Excess Cu stabilizes HIF-1α in the cytosol, but the HIF-1 transcriptional activity requires Cu. In the presence of physiologically relevant levels of Cu, hypoxia-induced activation of HIF-1 is secured and thus the expression of relevant genes is ensured. Under the physiological conditions, Cu does not play a role in the stability of HIF-1α in the cytosol, but is required to participate in the formation of HIF-1 transcriptional complex and in the interaction between the HIF-1 transcriptional complex and the HRE sequence. This role of Cu in the nucleus is more related to some undefined Cu-binding proteins although it was known that CCS is critically involved in the translocation of Cu from the cytosol to the nucleus.

Finally, not all of the genes regulated by HIF-1 require Cu for their expression under stress conditions (Zhang et al., 2014). Therefore, the requirement for Cu in the regulation of HIF-1 transcriptional activity most likely represents a mechanism for the fulfillment of specificity of HIF-1 regulation of gene expression under different conditions. All of these aspects of Cu regulation of the regression of pathological cardiac hypertrophy are the focused topics in this review.

2. Copper (Cu) and cardiac hypertrophy

2.1. Cardiac hypertrophy

Cardiac hypertrophy in some cases arises as an adaptive response to the increased workload (one of the major causes of hypertrophy) resulting from stimuli such as the increased pressure and volume overload. If the hypertrophic response is associated with the ultimate development of contractile dysfunction and heart failure, it is considered pathological (Hou & Kang, 2012). The pathological cardiac hypertrophy is characterized by depressed angiogenesis (Hamasaki et al., 2000; Karch et al., 2005; Shiojima et al., 2005; Huo et al., 2007), metabolic disorder (van Bilsen et al., 2004), increased interstitial fibrosis (Brilla & Maisch, 1994; Diez et al., 2001; Harada et al., 2007), and myocardial cell loss (Gottlieb et al., 1994; Olivetti et al., 1997; Takemura et al., 2013). In addition, cardiac hypertrophy is accomplished by re-expression of some fetal genes, such as atrial natriuretic peptide (ANP) (Holtwick et al., 2003), B-type natriuretic peptide (BNP) (McKie et al., 2010), and β-myosin heavy chain (β-MHC) (Tardiff et al., 2000; Pandya et al., 2006).

At the early stage of the pathogenesis of cardiac hypertrophy, the myocardium secretes angiogenic growth factors (Jiang et al., 2007; Dobaczewski et al., 2011), which stimulate coordinated vascular growth to meet the increased demand for blood supply due to the increase in myocardial mass and performance. Once the coordination between angiogenesis and cardiac hypertrophy is disrupted by sustained excessive demands, cardiac growth is driven along the pathological direction. Therefore, pathological cardiac hypertrophy is accompanied by enhanced coronary angiogenesis at the initial stage of the pathogenesis followed by the decrease in the capillary density in the late phase as a result of the depression of angiogenic growth factors. Among these