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Oxidation of cardiac myofilament proteins: Priming for dysfunction?

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ABSTRACT

Oxidants are produced endogenously and can react with and thereby post-translationally modify target proteins. They have been implicated in the redox regulation of signal transduction pathways conferring protection, but also in mediating oxidative stress and causing damage. The difference is that in scenarios of injury the amount of oxidants generated is higher and/or the duration of oxidant exposure sustained. In the cardiovascular system, oxidants are important for blood pressure homeostasis, for unperturbed cardiac function and also contribute to the observed protection during ischemic preconditioning. In contrast, oxidative stress accompanies all major cardiovascular pathologies and has been attributed to mediate contractile dysfunction in part by inducing oxidative modifications in myofilament proteins. However, the proportion to which oxidative modifications of contractile proteins are beneficial or causatively mediate disease progression needs to be carefully reconsidered. These antithetical aspects will be discussed in this review with special focus on direct oxidative post-translational modifications of myofilament proteins that have been described to occur *in vivo* and to regulate actin-myosin interactions in the cardiac myocyte sarcomere, the methodologies for detection of oxidative post-translational modifications in target proteins and the feasibility of antioxidant therapy strategies as a potential treatment for cardiac disorders.

Introduction

Oxidative stress describes the imbalance between the production of oxidants and the antioxidant capacity of the cell. This has been causally linked to cardiovascular pathologies such as hypertension (Montezano and Touyz, 2012; Rodrigo et al., 2011; Small et al., 2018), diabetes (Jia et al., 2018), ischemia/reperfusion (I/R) injury (Sun et al., 2018) and the development of heart failure (Bertero and Maack, 2018) in which contractile function deteriorates. However, endogenous oxidants are also crucial signaling molecules as they specifically and reversibly modify target proteins with impact on cardiovascular function (Burgoyne et al., 2007, 2015; Scotcher et al., 2016). Importantly, myofilament targets for oxidative modification in cardiac myocytes that form the basis of muscle contraction are actin and myosin, the key components of the thin and thick filament in the sarcomere, respectively. They are polymers organized in a myofibrillar lattice structure. It is very likely that polymeric myofilament structures may be more amenable to convert changes in post-translational modifications into a functional consequence than other globular proteins. Oxidation of a small proportion of a polymeric structure could potentially relay the oxidant-mediated signal onto the entire unit with a dramatic effect on a physiological function. In this context, reversible oxidative post-translational modifications of myofilament proteins that are crucially involved in excitation-contraction coupling could confer cardioprotective effects by limiting energy consumption important in a scenario such as hypertrophic cardiomyopathy associated with a hyper-contractile phenotype (Nag et al., 2017) or preventing hyper-oxidation at times of heightened cardiac oxidative stress. Thereby, reversibility of the oxidative modification might allow contractile recovery and prevent protein degradation, when the redox state of the cell returns to its normal state. However, when the oxidant burden during a disease condition remains high, structural modifications of the sarcomere affect cardiac function and promote the pathogenesis of heart failure.

This review provides an overview on thin and thick filament proteins that are susceptible to oxidation and how oxidative modifications impact on the regulation of the actin-myosin interaction.

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Abbreviations

ATP	Adenosine triphosphate
Cys	Cysteine
cMyBP-C	Cardiac myosin-binding protein C
DCM	Dilatated cardiomyopathy
F-actin	Filamentous actin
G-actin	Globular actin
GSSG	Glutahione disulphide
HALT-HCM	Hypertrophy Regression With N-Acetylcysteine in HCM
HCM	Hypertrophic cardiomyopathy
HNE	Trans-hydroxy-nonenal
IAM	Iodoacetamide
I/R	Ischemia/reperfusion
ICAT	Isotope-coded affinity tags
IodoTMT	Iodoacetyl tandem tags
MS	Mass spectrometry
NAC	N-Acetylcysteine
NEM	N-ethyl maleimide
oxPTM	Oxidative post-translational modification
PEG	Polyethylene glycol
ROS	Reactive oxygen species
Ser	Serine
TPM	Tropomyosin
Tn	Troponin

Methodologies for the detection of these oxidation events by biochemical or mass spectrometry analyses are discussed, as is the likelihood of antioxidant administration providing an effective therapy for contractile dysfunction during disease.

Regulation of the thin and thick filament

At the level of the sarcomere, development of force requires the promotion of actin-myosin interactions that are tightly controlled by regulatory proteins, intracellular Ca^{2+} concentration and fueled by energy from adenosine triphosphate (ATP) hydrolysis. At low intracellular Ca^{2+} concentrations, interaction of tropomyosin (TPM) and the heterotrimeric troponin complex (Tn), each of which are components of the thin filament, obscure the myosin binding sites on actin and thus prevent actin-myosin cross-bridges to form. When intracellular free Ca^{2+} increases, it binds to troponin C (TnC) and induces a conformational change in the TPM-Tn complex, together with movement of TPM on the thin-filament and exposure of the myosin-binding sites on actin (Solaro, 2010). The interaction of the myosin heads with actin is further controlled by cardiac myosin-binding protein C (cMyBP-C), a thick filament associated protein of the C-zone of sarcomeric A-bands (Fig. 1A). It acts as a brake on cross-bridge formation by binding to the myosin S2-domain (Carrier et al., 2015; Moss et al., 2015), providing steric hindrance to the myosin heads, which can be overcome by kinase-mediated phosphorylation of the N-terminal M-motif in cMyBP-C (Fig. 1B) (Gautel et al., 1995; Gruen et al., 1999). This potentiates cross-bridge formation and sliding of the thin filament relative to the thick filament under ATP-consumption allowing force development (Fig. 1B).

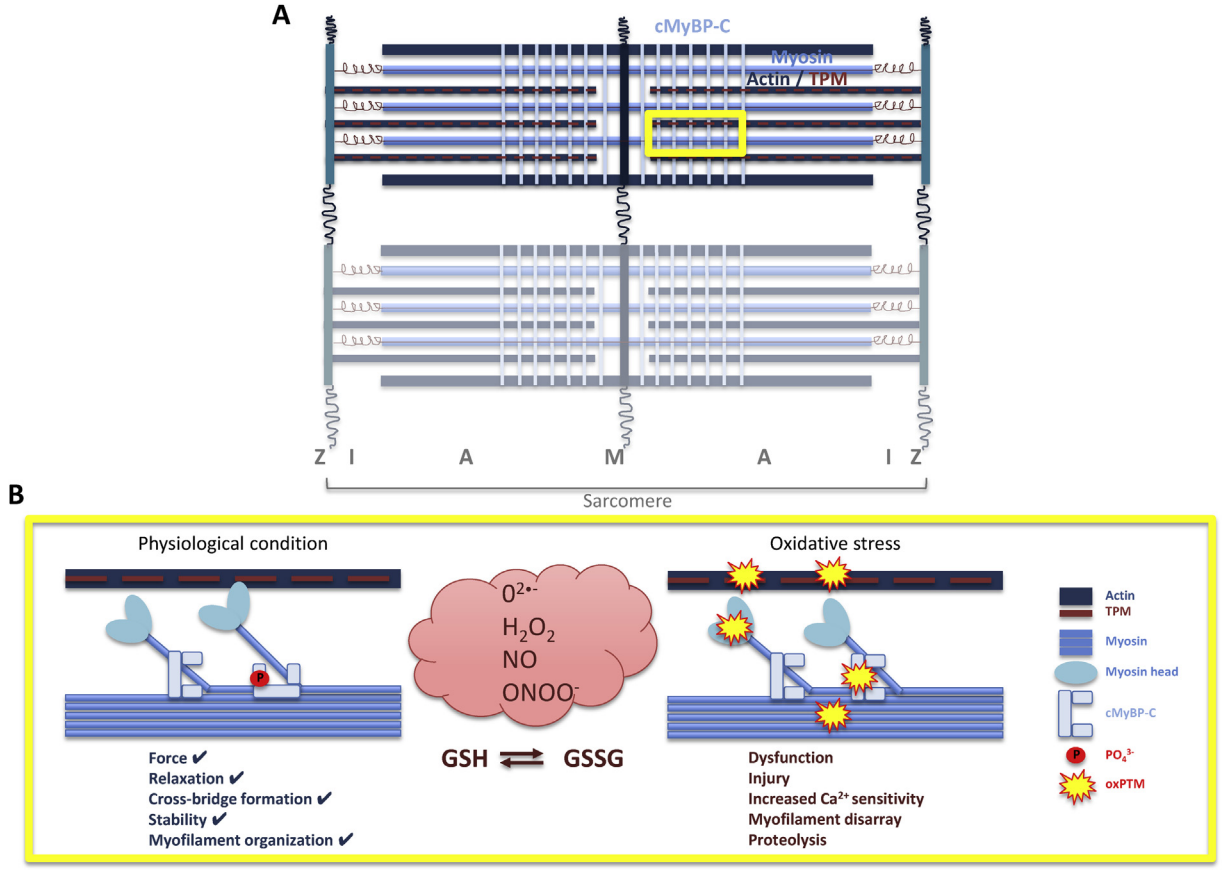

Fig. 1. Overview of the cardiac myocyte sarcomeric structure. A) Schematic overview of the sarcomere structure with Z- and M-line as well as I- and A-band and interdigitating thin actin-containing and thick myosin-containing filaments. **B)** Close-up of cross-bridge forming actin and myosin regulated by TPM and cMyBP-C during physiological conditions involving phosphorylation (**left panel**) and during conditions of oxidative stress (**right panel**).