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Metabolic Syndrome in Aging Heart: Molecular Insights

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Abstract

Risk factors that define the metabolic syndrome (MetS) develop with age increasing its prevalence. Therefore, MetS can be considered an age-related health problem. Mechanism involved in aging and MetS are incompletely understood. The goal of this review is to highlight novel molecular maladaptive mechanism that tiger cardiac disease and common in aging and MetS. We focus on mitochondrial energetic function as well as mitochondrial calcium handling. In addition, we analyzed the role of O-GlcNAcylation which is a posttranslational modification that triggers multiple signaling pathways.

Keywords: Aging; Heart; Metabolic syndrome; Molecular mechanisms; Mitochondrial calcium; O-GlcNAcylation

Introduction

Metabolic syndrome (MetS) is an arrangement of cardiovascular and metabolic risk factors that dramatically increase cardiovascular mortality and morbidity and type 2 diabetes [1-3]. MetS is a growing public health problem worldwide. The magnitude of the prevalence of MetS also signals to the complexity of the problem.

MetS is characterized by central obesity, dyslipidemia, compromised fasting glucose, and hypertension [4]. However, the pathophysiologic mechanisms that lead to MetS are incompletely understood.

The prevalence of MetS increases with age with cardiovascular disease being the most frequent outcome. Therefore, MetS can be considered an age-related disease.

Only after decades of intense research efforts worldwide we have identified important molecular targets of the aging process that lead to cardiovascular disease. We only describe some novel discoveries at the molecular level that revealed new therapeutic targets that have not been investigated.

Aging and decreased cardiac function

The process of general aging-related changes in model organisms has been explored recently [5-7]. The rate of aging is a controlled process governed by epigenetic pathways and biochemical processes which are conserved in evolution [6]. Aging is generally characterized by progressively impaired organ function and an increased propensity to death. This process indeed occurs in the heart. Of special relevance is that aging causes dysregulation of nutrient sensing, with abnormal metabolism and mitochondrial (Mito) dysfunction [5-7]. Though some studies have suggested that Reactive Oxygen Species (ROS) production may be implicated in the aging process, the role of ROS as a primary cause of cellular senescence has also been questioned [6,8]. Beyond these general concepts, it is clear that humans older than 65 years have an increased propensity for heart failure (HF) (e.g. 11/1000 persons) and that HF is enhanced further with increased age (e.g. 43/1000 in humans >80 years old) [9,10]. MetS further worsen these data. This is relevant since HF is always associated with recurrent hospitalization, decreased quality of life and a reduction in life span [11].

Alterations contributing to aging-related decreases in cardiac and Mito energetic function

The heart is a highly active metabolic organ which is very rich in Mito [12] and therefore susceptible to decreased Mito energetic function. Several converging mechanisms contribute to decreased Mito function with aging, including decreased Mito biogenesis, decreased Mito quality and decreased energetic function of Mito normalized for Mito quantity [6,13,14]. Some reports find no significant changes [14] and others find decreases in the function of specific Mito complexes and increased ROS production [13,15].

Mito Ca^{2+} handling, $[Ca^{2+}]$ m and Mito energetic function

Mito free calcium concentration ($[Ca^{2+}]$m) is an important signaling mechanism for Mito energetic activity by enhancing the activity of oxidative phosphorylation, especially complex III, and the Vmax of Complex V [16]. In addition, several dehydrogenases in the Mito matrix are activated by $[Ca^{2+}]$m including the Pyruvate Dehydrogenase Complex (PDC) which is the key enzyme for glucose oxidation (GOX) [17]. There are limited findings reported regarding aging-related changes in substrate consumption. A positron emission-based approach was used to show that myocardial glucose utilization could be stimulated by dobutamine, only in youn, but not old hearts [18]. Without an adequate compensatory increase in glucose utilization and GOX, a decrease in high-energy phosphate generation will prevail in the aging heart.

$[Ca^{2+}]$m is controlled by a complex set of mechanisms influencing Mito matrix Ca^{2+} uptake and release which have been reviewed [19,20]. Briefly, the outer Mito membrane (OMM) is quite Ca^{2+}-permeable [21], but import across the inner Mito membrane (IMM) is highly regulated. The most important contributor to Mito Ca^{2+} uptake

is the mitochondrial calcium uniporter complex (MCUC) with the MCU serving as a highly selective channel that moves Ca^{2+} ions across the IMM dependent on Mito membrane potential ($\Delta\Psi m$). Recently, integrative genomics methods enabled the discovery of the molecular nature of MCU, and its regulatory subunits, MCUb, MICU1 and 2, and EMRE [22-27]. MCU is an integral membrane protein with two transmembrane domains that forms the pore through which Mito Ca^{2+} currents are conducted across the IMM [22,23]. MCUb has been identified as a member of the oligmeric pore complex which reduces Mito channel activity [26]. MICU1 contains EF-hand Ca^{2+}-binding domains and is found in the Mito inter-membrane space (IMS), where it serves as a Ca^{2+}-sensing gatekeeper, keeping the channel closed when Ca^{2+} levels are low and allowing the channel to open in response to transient Ca^{2+} rises [28-30]. In addition MICU1 contributes to optimal coupling between cytosolic Ca^{2+} transients and activation of Mito-based Ca^{2+}-responsive dehydrogenases [28]. EMRE is a 10 kDa protein proposed to be essential for the in vivo uniporter current and additionally bridges the Ca2+-sensing role of MICU1 and MICU2 with the Ca^{2+}-conducting role of MCU [27].

Mito Ca^{2+} export is mediated by the Mito Na^{+}/Ca^{2+} Exchanger (mNCX) and the Mito H^{+}/Ca^{2+} Exchanger (mHCX) which have also been recently identified [31,32]. Short term opening of the Mito Permeability Transition Pore (MPTP) can also contribute to Mito Ca^{2+} release [33].

During the systolic and diastolic phase of a heartbeat, inter-myofibrillar Mito (IFM) which are in close proximity to the sarcoplasmic reticulum (SR), are exposed to the changing levels of the cytosolic Ca^{2+} transient. The cardiac myocyte cytosolic calcium concentration ($[Ca^{2+}]I$) increases from about 100nM during diastole, to about 500 nM in systole; however in the privileged micro-domain between the ryanodine receptor (RyR2) of the SR and the IFM, $[Ca^{2+}]I$ transiently rises to 10-20 μM during the systolic release phase of Ca^{2+} exiting the SR through the RyR2. Due to the relatively low affinity of MCU for Ca^{2+} the 20 to 40 fold higher $[Ca^{2+}]I$ levels, which persist for about 10ms during systole, are the most active time for Mito Ca^{2+} import by the MCUC [34]. The Mito Ca^{2+} transient follows the cytosolic Ca^{2+} transient with a slight delay, and a much smaller magnitude. Overall the Mito Ca^{2+} uptake accounts only for 1-2% of cytosolic Ca^{2+} extrusion [35,36]. The impact of Mito Ca^{2+} handling is therefore not so much linked to its contribution the cytosolic Ca^{2+} transients, but derives more from the importance of $[Ca^{2+}]m$ for Mito energetic function. The amount of Ca^{2+} that enters Mito via MCU or other mechanisms, must be extruded to an equal extent by Mito Ca^{2+} exporters like the mNCX [31]. Feedback loops exist that regulate increased Mito import and resultant increased Ca^{2+} release, so, as to potentially protect Mito against Ca^{2+} overload [37]. Excessive $[Ca^{2+}]m$ loading, as can occur with an acute ischemic event, can result in the opening of the MPTP complex with large amounts of Ca^{2+} released into the cytoplasm, ultimately leading to activation of cardiac myocyte death pathways [38].

Studies in mice with ubiquitous or CM-specific inducible deletions of MCU have generated interesting findings. Mice with a ubiquitous knock-out of MCU are viable and show decreased energetic efficiency and maximal performance of skeletal muscle [39]. Cardiac function was not evaluated in detail. Subsequent work with MCU KO mice generated in a C57BL/6 background showed mid-gestation lethality [40]. Recent reports indicate that β-adrenergic responsiveness [41] and the fight or flight response, is dependent on MCU activity [42]. Two recent reports using mice with conditional cardiac myocyte-specific deletion of MCU [43,44] found that MCU Ca^{2+} conductance activity matches energetic supply with cardiac workload during an acute stress mediated by β adrenergic stimulation [44]. It should be noted that the control mice and the mice with MCU deletion are in a normal "unstressed" physiological state, unless submitted to β adrenergic stimulation or a sprint exercise [43,44]. Old mice are known to be submitted to aging-related "stresses" including decreasing cardiac function and have difficulty responding to an increased demand for cardiac work [45]. This may lead to post-translational modifications of MCU or of other MCUC members impairing Mito Ca^{2+} conductance functions independent of acute β adrenergic stimulation. Other work has shown that post-translational modification of MCU by phosphorylation markedly enhances the Ca^{2+} conductance of MCU [46]. Using Tg mice with expression of a dominant negative form of MCU, no acute β adrenergic stimulus was needed for MCU to function as Mito Ca^{2+} importer [47]. A new report demonstrated that simulated hyperglycemia in cardiac myocytes reduces $[Ca^{2+}]m$, and glucose oxidation with an increase in fatty acid oxidation [18]. Furthermore. Diaz-Juarez et al. demonstrated in the same report that restoring [Ca2+]m concentration to normal levels by genetically expressing MCU normalized glucose and fatty acid metabolism in spite of simulated hyperglycemia. These findings point out a possible pathophysiological role of MCUC in simulated ischemia.

Excessive O-GlcNAcylation of CM and Mito proteins and Mito energetic function

O-GlcNAcylation of serine or threonine residues of nuclear, cytoplasmic and Mito proteins is a dynamic and ubiquitous protein modification [48-50]. This process has emerged as a key regulator of critical biological functions including transcription and translational processes [51], and of Mito function [52], as was also shown by prior work [53]. Post-translational protein modifications by phosphorylation (O-P) and O-GlcNAc can have reciprocal effects on protein function and are mediated by different types of dynamic interplays. In addition, competitive and alternate modification of adjacent sites occurs as well as other interactions [49]. Overall modification of protein function by O-GlcNAc derives from the interplay between protein modification by O-P and O-GlcNAc.

The O-GlcNAc status of proteins is regulated by O-GlcNAc transferase (OGT) and O-GlcNAcase (GCA), which catalyze the addition and removal of O-GlcaNAc residues, respectively [54-58]. The overall catalytic activity of OGT is positively controlled by the concentration of its donor substrate UDP-GlcNAc, making it an excellent metabolic sensor. OGT is O-GlcNAcylated and tyrosine-phosphorylated [49,56]. Recent evidence indicates that a shorter GCA splice variant, which has enzyme activity, occurs [59] and can be Mito-directed. Recently, several Mito proteins of the respiratory chain complex that undergo O-GlcNAcylation in the diabetic heart have been identified [53]. Interestingly, increased O-GlcNAcylation of cardiac proteins occurs in the aging heart [60].

Conclusions

It is currently unclear if the decrease in Mito energetic and metabolic function that occurs in the aging heart can be restored. Research is needed to explore this by using two novel interventions: 1) Rectifying $[Ca^{2+}]m$ through normalizing MCU levels and MCUC function, and 2) Reversing the excessive O-GlcNAcylation of cardiac myocytes and especially Mito proteins, including MCU. Currently no

data are available in the literature for Mito Ca^{2+} handling, $[Ca^{2+}]m$ or MCUC levels in cardiac myocytes from aging heart. Increased O-GlcNAcylation of cardiac myocyte proteins from aging heart has been reported [60], but no attempt has been made to reverse the excessive Mito protein O-GlcNAcylation of aging heart and determine if this can improve cardiac function in aging heart. Assuming that these questions can be answered, innovative therapeutic approaches for the declining function of the aging heart and its increased propensity to develop heart failure may result.

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