

# Metabolic Syndrome and Role of Mitochondrial Calcium Handling

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## Editorial

Metabolic syndrome (MetS) is a growing public health problem worldwide. MetS prevalence in the United States has been investigated recently. The article in this journal by Miller and Fridline [1] reported a prevalence of MetS in the total studied cohort of  $34.7 \pm 1.4\%$ . The risk factor with the highest proportion and risk for the total sample and by sex was waist circumference (WC). Women had a higher prevalence of WC, HDL, and blood pressure risk factors compared to men who had a higher prevalence of triglycerides and fasting plasma glucose [1]. Furthermore, MetS is an arrangement of cardiovascular and metabolic risk factors that dramatically increase cardiovascular mortality and morbidity and type 2 diabetes [2-4]. These alarming data emphasize the importance of MetS as an epidemic and dangerous disease. 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 [5]. However, the pathophysiologic mechanisms that lead to MetS are incompletely understood. It is well accepted that genetic and environmental factors determine the development of MetS. Therapeutic approaches to modify life style to correct MetS are established. Nevertheless, the prevalence of MetS increases worldwide. Therefore, there is an extraordinary need for innovative therapeutic approaches.

Mitochondria play central roles in energy metabolism, cell signaling and apoptosis regulation. It has been proposed that dysfunctional mitochondria may contribute to the development of metabolic disorders [6].

Mitochondrial abnormalities associated with MetS target genetic factors, mitochondrial morphology, oxidative phosphorylation,  $\text{Ca}^{2+}$  handling and ROS, mitochondrial dysfunction and insulin signaling [7]. Therefore, mitochondria are a natural target for metabolic disorders [7]. The question is: can we repair the dysfunctional mitochondria? Possibly yes.

Mitochondrial free  $\text{Ca}^{2+}$  concentration ( $[\text{Ca}^{2+}]_m$ ) is a mayor modulator of mitochondrial metabolism and energy production.  $[\text{Ca}^{2+}]_m$  is governed by a complex set of mechanisms influencing mitochondrial matrix  $\text{Ca}^{2+}$  uptake and release which have been reviewed [8,9]. Briefly, the outer mitochondrial membrane (OMM) is quite  $\text{Ca}^{2+}$  permeable [10], but import across the inner mitochondrial membrane (IMM) is highly regulated. An important contributor to mitochondrial  $\text{Ca}^{2+}$  uptake is the mitochondrial  $\text{Ca}^{2+}$  uniporter complex (MCUC) with the mitochondrial  $\text{Ca}^{2+}$  uniporter (MCU) serving as a highly selective channel that moves  $\text{Ca}^{2+}$  ions across the IMM dependent on mitochondrial membrane potential ( $\Delta\psi_m$ ). Although this information has been known for decades, only recently,

integrative genomics methods enabled the discovery of the molecular nature of the uniporter pore of MCUC, and its regulatory subunits, MCUb, MICU1 and MICU2, and EMRE [11-16]. However, the physiological role of the MCUC remains controversial [17]. A new report demonstrated that simulated hyperglycemia in cardiac myocytes reduces  $[\text{Ca}^{2+}]_m$ , and glucose oxidation with an increase in fatty acid oxidation [18]. Furthermore, Diaz-Juarez et al. demonstrated in the same report that restoring  $[\text{Ca}^{2+}]_m$  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 hyperglycemia. However, abnormalities in mitochondrial  $\text{Ca}^{2+}$  handling in obesity, MetS or diabetes are incompletely investigated. While metabolic abnormalities in MetS are well established the pathophysiologic mechanisms involved remain unknown. We do not know whether mitochondrial  $\text{Ca}^{2+}$  handling plays a role and whether correcting mitochondrial  $\text{Ca}^{2+}$  handling will improve these metabolic disorders.

Certainly the prevalence of MetS is alarming, however, new therapeutic approaches that are arising bring hope to people fighting this disease.

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