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Metabolic Syndrome and Mitochondrial Transcription Factor A

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Dear Editor,

Metabolic syndrome (MS) represents a cluster of cardiovascular risk factors (obesity, hypertension, dyslipidemia and insulin resistance) associated with increased cardiovascular morbidity and mortality. The genetic basis of MS is still unknown and very important to be determined because of constantly increasing prevalence of MS worldwide, which is primarily due to epidemic obesity. Mitochondrial transcription factor A (TFAM) plays an essential role in direct regulation of mitochondrial genome, affecting transcription initiation and replication (1). Age-related modifications of oxidative stress could impact mitochondrial DNA replication by regulating the TFAM activity in type II diabetes (2). Although the role of adipose tissue mitochondria in development of these disorders is unknown, studies have found mitochondrial dysfunction in adipose tissue in regard with obesity and type II diabetes (1, 3). According to the investigators, TFAM has an important function in insulin resistance development which represents a cornerstone of MS.

A recent investigation showed that TFAM deletion in the adipose tissue increased mitochondrial oxidation, resulting in positive metabolic effects, suggesting that regulation of adipose tissue mitochondria could represent a potential therapeutic target for treatment of obesity (4). Additionally, the studies have shown that metabolic memory phenomenon could disable the normal membrane transportation in type II diabetes. Impaired transfer of TFAM to mitochondria, and reduced linkage between TFAM and mitochondrial DNA resulted in deficient mitochondrial transcription (5). Even after normalization of the blood glucose level, these processes remained dysfunctional, confirming the theory of metabolic memory phenomenon.

Wang et al. found that higher levels of intracellular reactive oxygen species caused by mitochondrial dysfunction resulted in: (i) deterioration of adipocytes functions in preserving the glucose metabolism by decreasing the insulin signaling; (ii) down-regulation of glucose transporter expression; and (iii) decrease in adiponectin secretion (6). These findings demonstrated the significant role of mitochondria in maintenance of glucose homeostasis in adipocytes and additionally offered a molecular mechanism for explaining the complication of diabetes mellitus or insulin resistance.

Holmstrom et al. tested the association between the tissue-specific role of mitochondrial respiratory capacity as well as development of insulin resistance and type II diabetes, using animal models (7). The authors found that TFAM levels decreased in obese diabetic mice, together with increased level of proteins associated with mitochondrial dynamics. The investigators concluded that insulin resistance in liver and skeletal muscle in obese diabetic mice corresponded to mitochondrial dysfunction (7).

In the previous issue of "Gene, Cell and Tissue", Hashemi et al. investigated the association between TFAM and MS (8). They hypothesized that correlation between TFAM and MS existed due to the previously detected relationship between TFAM and insulin resistance and diabetes. The investigators included 151 patients with and 149 without MS. They reported that the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria were used for definition of MS; however, authors did not define other inclusion and exclusion criteria, which could be very significant for the final results. It was essential to report the number of patients with coronary artery disease, diabetes or heart failure, since these are important confounding factors affecting TFAM expression (2, 9). In addition, the number of patients treated due to hypertension, diabetes or dyslipidemia was unclear. Notably, the number of women was two folds higher than men in both control and MS groups. Indeed, there was no difference in gender distribution between the control and MS groups; how-

ever, a recent analysis showed a sex dimorphism regarding the age-associated defects in cardiac mitochondrial function (10), which emphasized on the importance of equal sex distribution in TFAM expression investigations. Furthermore, the researchers did not separate the study subjects to different age groups, which could be helpful in differentiation of TFAM promoter methylation. Perhaps, age distribution could provide a better insight into mitochondrial transcription changes of the study population.

The authors concluded that there was no association between TFAM promoter methylation and MS (10). Disregarding the aforementioned limitations, there could be several possible reasons for those rather unexpected result. First, MS represents a cluster of cardiovascular risk factors, not only obesity and diabetes, and the interaction pathways of arterial hypertension and dyslipidemia with TFAM are still unknown. Second, it is still not identified whether there is an association between promoter TFAM methylation and the number of MS criteria. Third, this investigation was conducted among an Iranian population. This raises the issue of possible influence of ethnicity and environment on promoter TFAM methylation.

Further studies with larger numbers of subjects, equal gender distributions, and inclusion of MS subjects without comorbidities such as coronary artery diseases, diabetes and heart failure, will provide more detailed information about the relationship between TFAM methylation and MS.

Authors' Contributions

Marijana Tadic: interpretation of data and drafting of the manuscript; Cesare Cuspidi: critical revision of the manuscript for important intellectual content.

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