Metabolic Syndrome Research and Therapeutics

Subjects: Endocrinology & Metabolism

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Metabolic syndrome (MetS) is a well-defined yet difficult-to-manage disease entity. Both the precipitous rise in its incidence due to contemporary lifestyles and the growing heterogeneity among affected populations present unprecedented challenges.

Keywords: metabolic syndrome ; metabolomics ; microbiota ; precision medicine ; proteomics

1. Introduction

Metabolic syndrome (MetS) is classically recognized as a cluster of at least three of the five following conditions: central obesity, hypertension, hyperglycemia, hypertriglyceridemia, and low serum high-density lipoprotein [1][2][3]. The etiologies are proposed to be multi-factorial, including diet pattern, genetic predisposition, ethnicity, etc. The MEDLIFE index is an assessment based on Mediterranean lifestyle, including food choice, exercise, and social interaction. Although ascertaining the exact prevalence of MetS remains a challenge, epidemiological studies have suggested that over one billion individuals worldwide suffer from MetS, and the value is in constant escalation, given lifestyle modifications secondary to urbanization in modern society [4].

The clinical characteristics of MetS subsequently induce plaque rupture and bring about thromboembolic event. Multi-site arterial calcification observed in MetS patients has been shown to predict cardiovascular events and coronary disease. In addition to established cardiovascular mortality, the presence of MetS is correlated with an increased risk of sudden cardiac death, as shown by Hess et al., who analyzed 13,168 American patients from the Atherosclerosis Risk in Communities Study database with 23.6 years of follow up. Glomerular hyperfiltration, eventual chronic kidney disease, and excessive mortality rate, were found to be associated with non-alcoholic fatty liver disease in MetS hosts [5][6].

2. Proteomics

Although the human genome contains approximately 20,300 genes, differential transcription, splicing, amino acid polymorphisms, and post-translational modification (e.g., methylation, acetylation, phosphorylation, and glycosylation) can result in more than 100 different functional products. Similar to metabolomics, proteomic studies uncover the orchestration of the differential abundance of protein products, which thereafter influences the homeostasis of host energy utilization [7]. In conjunction with genomic research, these investigations attempt to elucidate the molecular network and identify possible therapeutic targets. Here, we review the recent advances in proteomic research on MetS (**Table 2**).

Albeit in the presence of adaptive responses, perturbations in mitochondrial physiology predisposed subjects to the development of cardiometabolic comorbidities [8]. A recent study using muscle biopsy demonstrated dominant proteolysis, diminished oxidative phosphorylation, and impaired clearance of reactive oxygen species in this population [9]. Distinguishing proteomic alterations is central to understanding the pathogenesis of MetS. Author, YearSpeciesCohortFindingsRefHsieh, 2016AnimalMale Sprague Dawley ratsHigh-fructose diet escalates oxidative stress, disturbing glucose and fatty acid metabolism.[10]Benade, 2020Male Wistar ratsAltered mitochondrial physiology predisposes cardiometabolic complications.[8]Markova, 2019Male hereditary hypertriglyceridaemic ratsDicarbonyl stress aggravated by methylglyoxal, causing renal dysfunction in MetS.[11]Conceição,

Study of proteomics. MetS, metabolic syndrome.

To investigate the influence of protein signatures on cellular behavior, proteomic studies of visceral adipose tissue from metabolically unhealthy obese patients have illustrated that pathways related to cell migration, development of the hematological system, and immune cell trafficking can be drastically impacted [12]. The static status was assessed, the dynamics of proteomic evolvement carries clinical implications as well. For example, supplementation of hesperidin

strongly modified protein expression in rodent heart and renal tissues, thereby re-conditioning the risk of downstream complications [13]. Further, exogenous stimuli were documented to be memorized by proteomic imprinting and thereby exerted a legacy effect.

3. Microbiota and Inflammation

The status of inflammation has been well-recognized in MetS, as well as consequential complications established to be the consequence. Although there is argument that the metabolites related to insulin resistance and those associated with cardiovascular prognosis bore little resemblance [14], the effect exerted by altered intestinal microbiomes in response to exogenous stimuli still impacts the host [15]. Interestingly, the landscape of gut microbiota was transiently reshaped with diet and steroid-induced imprint of inflammation, hepatic steatosis, and insulin sensitivity in the porcine model. In this section, we revisit investigations regarding microbiota and inflammation (**Table 3**).

Pioneering evidence based on animal models featuring germ-free mice and obese (OB/OB) rodents have demonstrated specific microbial compositions in the setting of MetS, DM, atherosclerosis, non-alcoholic liver disease, hypertension, etc. Impaired intestinal barriers permit the translocation of bacteria and their components from the gastrointestinal lumen into the bloodstream [16][17]. Meanwhile, through the infiltration of gut microbiota, obesity leads to the downregulation of JNK and PPARG, causing insulin resistance. However, through the advancement in sample harvesting and viability assessment for bacterial components of interest, MetS was further validated to be highly associated with inflammation in vivo [18].

Metabolic disruption is also coordinated via small molecules generated by gut flora. Short-chain fatty acids (SCFA) are produced from hydrolysis and subsequent fermentation of consumed polysaccharides by intestinal microbiota. SCFA affects satiety through peptide YY and glucagon-like peptide 1 (GLP-1) In addition, SCFA is involved in fatty acid oxidation, lipogenesis, and energy utilization [19].

Finally, gut dysbiosis compromises host metabolism. Some human studies have attributed obesity to a combination of reduced bacterial populations of anti-inflammatory Bifidobacterium, butyrate-producing Akkermansia muciniphila, Actinobacteria, and Bacteriodes, in addition to the dominant presence ofEscherichia coli, Staphylococcus aureus, Enterobacteriaceae, as well as pathogenic Campylobacter and Shigella [20]. Metagenomic analysis argued that quantitative diversity and the functional alteration of gut microbiota synergistically determine metabolic phenotype [21]. In summary, endotoxemia, inflammatory predicament, small molecule signaling disruptions, and unbalanced composition of gut flora play primary roles in the pathogenesis of MetS.

4. Novel Treatments

Enhanced dissection of the molecular configurations has augmented the advancement of therapeutic schemes. In contrast to the conventional one-for-all management protocols, precision medicine designs individualized recipes by taking personal molecular features into account. Traditional non-pharmaceutical approaches against MetS included diet modification, aerobic exercise, and psychological management, whereas medication was administered primarily for the prevention or treatment of comorbidities. We proposed two novel treatment modalities, fecal microbiota transplantation (FMT) and targeting end products of cholesterol catabolism (**Table 4**).

Consumption of probiotics was illustrated to attenuate insulin resistance and DM in mice feeding on high fat diet [22]. In addition to direct supplementation of microspecies, FMT was introduced to potentially reorganize endogenous bacterial formation. Targeting the end products of cholesterol catabolism is another potential means to antagonize MetS. Accordingly, approaches to manipulate the physiology of bile acid may impede MetS.

Subsequently, Smits et al. randomly assigned 20 obese and insulin-resistant males with MetS to receive FMT either from single lean vegan donor or autologously [23]. Although allogenic FMT was demonstrated effective in enhancing small intestine permeability in patients with nonalcoholic fatty liver disease [24], no randomized trial has examined FMT efficacy on MetS to date, and relevant human studies are scarce. systematically reviewed the efficacy of FMT on MetS, demonstrating pronounced improvement in insulin sensitivity and reduced HbA1C levels [25]. On the other hand, other clinical parameters, e.g., BMI, fasting plasma glucose, and triglyceride, showed no significant differences.

Another aspect of the consequences from gut dysbiosis in MetS involves the regulation of bile acid [26]. Secreted by the liver as the end product of cholesterol catabolism, bile acids participate in intestinal nutrient absorption, and are determinants for gut microbiota growth. Extensive research has set out to define the functional role of bile acid against

MetS, not only as it is closely intertwined with gut microbiota, as it has bacteriostatic effects and mucosal protection in the small intestine [27], but also due to its integrative role in lipid synthesis. Preferentially through 12α-hydroxylation, enhanced synthesis and obtuse postprandial elevation of bile acid was observed in obese subjects [28].

A total of 25 previously healthy subjects who followed fast food diets manifested elevated serum bile acid levels, markers of hepatic injury, and impacted metabolic panels [29]. In addition, the modulating effect on circadian rhythm by bile acid metabolism has been well-established. Disturbed lifestyle and irregular diet habits disrupt circadian rhythm, rattle gluconeogenesis, lipogenesis, and bile acid metabolism, ultimately leading to MetS [30]. However, the side effects of medications which manipulate bile acid metabolism, such as pruritus, remain problematic as they perpetuate noncompliance.

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