Editorial

Obesity: causes, consequences, treatments, and challenges

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Obesity has become a global epidemic and is one of today's most public health problems worldwide. Obesity poses a major risk for a variety of serious diseases including diabetes mellitus, non-alcoholic liver disease (NAFLD), cardiovascular disease, hypertension and stroke, and certain forms of cancer (Bluher, 2019).

Obesity is mainly caused by imbalanced energy intake and expenditure due to a sedentary lifestyle coupled with overnutrition. Excess nutrients are stored in adipose tissue (AT) in the form of triglycerides, which will be utilized as nutrients by other tissues through lipolysis under nutrient deficit conditions. There are two major types of AT, white AT (WAT) and brown AT, the latter is a specialized form of fat depot that participates in non-shivering thermogenesis through lipid oxidation-mediated heat generation. While WAT has been historically considered merely an energy reservoir, this fat depot is now well known to function as an endocrine organ that produces and secretes various hormones, cytokines, and metabolites (termed as adipokines) to control systemic energy balance. Studies over the past decade also show that WAT, especially subcutaneous WAT, could undergo 'beiging' remodeling in response to environmental or hormonal perturbation. In the first paper of this special issue, Cheong and Xu (2021) systematically review the recent progress on the factors, pathways, and mechanisms that regulate the intercellular and inter-organ crosstalks in the beiging of WAT. A critical but still not fully addressed issue in the adipose research field is the origin of the beige cells. Although beige adipocytes are known to have distinct cellular origins from brown and while adipocytes, it remains unclear on whether the cells are from pre-existing mature white adipocytes through a transdifferentiation process or from *de novo* differentiation of precursor cells. AT is a heterogeneous tissue composed of not only adipocytes but also nonadipocyte cell populations, including fibroblasts, as well as endothelial, blood, stromal, and adipocyte precursor cells (Ruan, 2020). The authors examined evidence to show that heterogeneity contributes to different browning capacities among fat depots and even within the same depot. The local microenvironment in WAT, which is dynamically and coordinately controlled by inputs from the heterogeneous cell types, plays a critical role in the beige adipogenesis process. The authors also examined key regulators of the AT microenvironment, including vascularization, the sympathetic nerve system, immune cells, peptide hormones, exosomes, and gut microbiota-derived metabolites. Given that increasing beige fat function enhances energy expenditure and consequently reduces body weight gain, identification and characterization of novel regulators and understanding their mechanisms of action in the beiging process has a therapeutic potential to combat obesity and its associated diseases. However, as noticed by the authors, most of the current preclinical research on 'beiging' are done in rodent models, which may not represent the exact phenomenon in humans (Cheong and Xu, 2021). Thus, further investigations will be needed to translate the findings from bench to clinic.

While both social–environmental factors and genetic preposition have been recognized to play important roles in obesity epidemic, Gao et al. (2021) present evidence showing that epigenetic changes may be a key factor to explain interindividual differences in obesity. The authors examined data on the function of DNA methylation in regulating the expression of key genes involved in metabolism. They also summarize the roles of histone modifications as well as various RNAs such as microRNAs, long noncoding RNAs, and circular RNAs in regulating metabolic gene expression in metabolic organs in response to environmental cues. Lastly, the authors discuss the effect of lifestyle modification and therapeutic agents on epigenetic regulation of energy homeostasis. Understanding the mechanisms by which lifestyles such as diet and exercise modulate the

expression and function of epigenetic factors in metabolism should be essential for developing novel strategies for the prevention and treatment of obesity and its associated metabolic diseases.

A major consequence of obesity is type 2 diabetes, a chronic disease that occurs when body cannot use and produce insulin effectively. Diabetes profoundly and adversely affects the vasculature, leading to various cardiovascular-related diseases such as atherosclerosis, arteriosclerotic, and microvascular diseases, which have been recognized as the most common causes of death in people with diabetes (Cho et al., 2018). Love et al. (2021) systematically review the roles and regulation of endothelial insulin resistance in diabetes complications, focusing mainly on vascular dysfunction. The authors review the vasoprotective functions and the mechanisms of action of endothelial insulin and insulin-like growth factor 1 signaling pathways. They also examined the contribution and impart of endothelial insulin resistance to diabetes complications from both biochemical and physiological perspectives and evaluated the beneficial roles of many of the medications currently used for T2D treatment in vascular management, including metformin, thiazolidinediones, glucagon-like receptor agonists, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter inhibitors, as well as exercise. The authors present evidence to suggest that sex differences and racial/ethnic disparities contribute significantly to vascular dysfunction in the setting of diabetes. Lastly, the authors raise a number of very important questions with regard to the role and connection of endothelial insulin resistance to metabolic dysfunction in other major metabolic organs/tissues and suggest several insightful directions in this area for future investigation.

Following on from the theme of obesity-induced metabolic dysfunction, Xia et al. (2021) review the latest progresses on the role of membrane-type I matrix metalloproteinase (MT1-MMP), a zinc-dependent endopeptidase that proteolytically cleaves extracellular matrix components and non-matrix proteins, in lipid metabolism. The authors examined data on the transcriptional and post-translational modification regulation of MT1-MMP gene expression and function. They also present evidence showing that the functions of MT1-MMP in lipid metabolism are cell specific as it may either promote or suppress inflammation and atherosclerosis depending on its presence in distinct cells. MT1-MMP appears to exert a complex role in obesity for that the molecule delays the progression of early obesity but exacerbates obesity at the advanced stage. Because inhibition of MT1-MMP can potentially lower the circulating low-density lipoprotein cholesterol levels and reduce the risk of cancer metastasis and atherosclerosis, the protein has been viewed as a very promising therapeutic target. However, challenges remain in developing MT1-MMP-based therapies due to the tissue-specific roles of MT1-MMP and the lack of specific inhibitors for this molecule. Further investigations are needed to address these questions and to develop MT1-MMP-based therapeutic interventions.

Lastly, Huang et al. (2021) present new findings on a critical role of puromycin-sensitive aminopeptidase (PSA), an integral non-transmembrane enzyme that catalyzes the cleavage of amino acids near the N-terminus of polypeptides, in NAFLD. NAFLD, ranging from simple nonalcoholic fatty liver to the more aggressive subtype nonalcoholic steatohepatitis, has now become the leading chronic liver disease worldwide (Loomba et al., 2021). At present, no effective drugs are available for NAFLD management in the clinic mainly due to the lack of a complete understanding of the mechanisms underlying the disease progress, reinforcing the urgent need to identify and validate novel targets and to elucidate their mechanisms of action in NAFLD development and pathogenesis. Huang et al. (2021) found that PSA expression levels were greatly reduced in the livers of obese mouse models and that the decreased PSA expression correlated with the progression of NAFLD in humans. They also found that PSA levels were negatively correlated with triglyceride accumulation in cultured hepatocytes and in the liver of *ob/ob* mice. Moreover, PSA suppresses steatosis by promoting lipogenesis and attenuating fatty acid β-oxidation in hepatocytes and protects oxidative stress and lipid overload in the liver by activating the nuclear factor erythroid 2-related factor 2, the master regulator of antioxidant response. These studies identify PSA as a pivotal regulator of hepatic lipid metabolism and suggest that PSA may be a potential biomarker and therapeutic target for treating NAFLD.

In summary, papers in this issue review our current knowledge on the causes, consequences, and interventions of obesity and its associated diseases such as type 2 diabetes, NAFLD, and cardiovascular disease (Cheong and Xu, 2021; Gao et al., 2021; Love et al., 2021). Potential targets for the treatment of dyslipidemia and NAFLD are also discussed, as exemplified by MT1-MMP and PSA (Huang et al., 2021; Xia et al., 2021). It is noted that despite enormous effect, few pharmacological interventions are currently available in the clinic to effectively treat obesity. In addition, while enhancing energy expenditure by browning/beiging of WAT has been demonstrated as a promising alternative approach to alleviate obesity in rodent models, it remains to be determined on whether such WAT reprogramming is effective in combating obesity in humans (Cheong and Xu, 2021). Better understanding the mechanisms by which obesity induces various medical consequences and identification and characterization of novel anti-obesity secreted factors/soluble molecules would be helpful for developing effective therapeutic treatments for obesity and its associated medical complications.

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