OPEN

Experimental & Molecular Medicine (2016) 48, e214; doi:10.1038/emm.2015.119

www.nature.com/emm

EDITORIAL

Dynamic cross talk between metabolic organs in obesity and metabolic diseases

Experimental & Molecular Medicine (2016) **48,** e214; doi:10.1038/emm.2015.119; published online 11 March 2016

During evolution, living organisms have adapted to utilize various nutrient sources, including carbohydrates, lipids and proteins. In particular, carbohydrates and lipids are the two major macromolecules serving as key components of intracellular storage products for energy generation. Importantly, anabolism and catabolism of these macromolecules are closely interwoven in organs involved in nutrient regulation, including the brain, liver, adipose tissue, pancreas and muscle. Among numerous organs and tissues, adipose tissues have key regulatory roles in survival, reproduction and adaptation to nutritional stresses by way of their functioning as a storage depot. For instance, adipose tissues actively expand in response to excess energy intake and generate energy sources in response to nutrient deficit, promptly engaging in the control of systemic energy balance. In addition, adipose tissues communicate with other metabolic organs through secreting various adipokines, exerting multiple impacts on the regulation of systemic energy homeostasis.

Over the past few decades, the rate of obesity has grown rapidly around the world, imposing a high social burden in terms of quality of life. Mounting evidence suggests that obesity is closely associated with the development of metabolic syndrome, including hyperlipidemia, hypertension, cardiovascular diseases, insulin resistance, hypercholesterolemia, type 2 diabetes and even certain types of cancer. A hallmark of obesity is excessive expansion of body fat that is attributable to chronic energy intake and sedentary lifestyle. Given the significant role of cross talk between adipose tissues and other metabolic organs related to the regulation of whole-body energy homeostasis, defining inter-organ metabolic communication involved in energy homeostasis would broaden the understanding of complex systems contributing to obesity. In this special issue, we will discuss recent findings on the cellular and molecular mechanisms in the cross talk of key metabolic organs, including the brain, heart, liver, adipose tissue and pancreas, and their roles in the control of energy metabolism, as well as etiology of obesity. We also highlight the new findings from genetic and epigenetic studies on obesity and its related diseases such as insulin resistance.

Aimin Xu's group (Hong Kong University) provides a comprehensive review of adipose tissue and its potential clinical implications. They have discussed the distinct characteristics of fat depots including white adipose tissue, brown adipose tissue and beige adipose tissue. There appear to be fat depot differences in cellular composition and physiological property as a result of genetic or developmental events. Upon developmental cues, hormonal changes, metabolic stresses and aging, distinct fat depots exhibit differences in their responses, as well as subsequent effects on energy metabolism, insulin sensitivity and thermogenesis. For instance, compared with subcutaneous adipose tissue, visceral adipose tissue is prone to become chronically inflamed and insulin resistant in obesity. They also provide insight into the potential role of adipose depot specificity in mediating paradoxical phenotypes of two populations—obese but metabolically healthy individuals and lean but metabolically unhealthy individuals.

It is well established that the brain has an important role in the regulation of energy homeostasis by way of assessing the current state of metabolism and energy homeostasis, and orchestrating modulation of both behavioral patterns and peripheral metabolism. Various nutrients and hormones derived from adipose tissue, pancreas, stomach, intestines and liver convey information regarding the metabolic state to multiple areas of the brain. After integrating peripheral metabolic, endocrine and neuronal signals, outflow pathways from the brain regulate food intake and energy expenditure. Particularly, Min-Seon Kim's group (Asan Medical Center and University of Ulsan) has focused on the critical role of the hypothalamus in the control of energy balance and obesity. Given the fact that coordinated interactions between hypothalamus and peripheral metabolic organs engage in governing whole-body energy homeostasis, defective signals from brain are closely linked to the detrimental effects of obesity in relation to energy metabolism.

Recent findings have revised the concept of adipose tissues being a mere energy reservoir. Instead, adipose tissues are endocrine organs that synthesize and secrete various signaling molecules, the so-called adipokines. Accordingly, an increase

or a decrease in adiposity affects the circulating levels of adipokines, leading to subsequent changes in systemic energy homeostasis by modulating the energy metabolism in other organs. Similarly, recent studies on the heart reveal that heart is another endocrine organ. Gary Sweeny's group (York University) has highlighted the recent findings on cardiac remodeling mediated by cardiokines with multiple impacts on peripheral tissues. As a model system, they have focused on myocardial inflammation in heart failure and underscored the critical role of cardiokines in the modulation of cross talk between heart and other tissues.

Liver is one of the primary sites of energy storage and is a central organ in glucose and lipid metabolism. Excess energy from the diet is stored in the form of glycogen in the liver, and once glycogen depots are full any additional excess energy is piled in the form of lipid in adipose tissue. Moreover, liver has an essential role in the complex network of systemic energy metabolism by acting as the major organ of glucose metabolism including glycogenesis, glycogenolysis, glycolysis and gluconeogenesis. Various metabolites and hormones tightly regulate hepatic glucose metabolism by modulating elaborated transcriptional networks. Therefore, Seung-Hoi Koo's group (Korea University) discusses the current understanding of hepatic energy homeostasis, particularly, with respect to key transcription factors and cofactors that are critical regulators of glucose and lipid metabolism.

Insulin and glucagon are essential hormones to regulate whole-body glucose and lipid metabolism, and both hormones are produced in the pancreas. Weiping Han's group (SBIC and A-STAR) provides an overview of pancreas development and its roles in glucose metabolism. They underscore the critical role of external cues, including gut hormones, nutrients, cellular metabolites and ions in the development of the pancreas. They also discuss the molecular events underlying variable interplay between the pancreas and other organs including, the brain, gut and liver, to coordinate whole-body energy metabolism. In addition, current therapeutic and putative targets for the treatment of type 2 diabetes are discussed.

Soo Heon Kwak and Kyong Soo Park (Seoul National University Hospital) provide an overview of the current findings from genetic and epigenetic studies regarding type 2 diabetes. Despite type 2 diabetes being caused by multiple factors, recent genetic association studies strongly suggest that certain genetic variations are closely linked with the incidence of type 2 diabetes. In addition to genetic factors, environmental cues also contribute to the development of type 2 diabetes by modulating epigenetic regulation, including DNA methylation, histone modification and non-coding RNAs. They discuss the plausible interactions between environmental factors, genetics and epigenetics to mediate pathogenesis of type 2 diabetes.

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