Unraveling complexity of interconnected regulatory circuits in lipid metabolism

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In this issue of *Journal of Biomedical Research*, 3 review articles are published that cover a broad range of topics addressing current understanding on regulation of nutrient metabolism through protein phosphatases, homeostatic regulation of cellular lipid droplets by small GTPases, and mechanisms by which hepatic assembly and secretion of triglyceride-rich lipoproteins are regulated.

Protein phosphorylation plays a central role in insulin and leptin signaling and is tightly synchronized by activities of protein kinases and phosphatases. Dysregulation of protein phosphorylation has been linked to aberrant energy metabolism including obesity and type 2 diabetes. Great emphasis has been placed on defining levels and activity of protein kinases in the pathology. However, kinase activity represents only one facet of the system responsible for regulating protein phosphorylation. A family of protein phosphatases, catalyzing de-phosphorylation at tyrosine or threonine/serine residues, plays a critical role in target phospho-regulation at tissue, cellular and subcellular levels. In the context of insulin and leptin signaling, protein tyrosine phosphatases contribute to coordinated regulation of both pathways in a complex, substrate-selectivity manner. Comparing to our knowledge on how regulation of kinase activity contributes to various disease, phosphatase activity and its regulation in disease remain less well understood. In the article titled “Metabolic regulation by protein tyrosine phosphatases”^[1], Knobler and Elso have presented a comprehensive overview of current data demonstrating the

intricate regulatory mechanisms conferred by protein tyrosine phosphatases in modulating the multipronged insulin and leptin signaling.

Obesity, chiefly as a result of excess caloric intake, increases the risk of mortality in men and women. Abnormalities in lipid metabolism, both in central and ectopic fat depots, represent the major contributor to metabolic syndrome including type 2 diabetes. Manifestation of insulin resistance and hyperglycemia is considered secondary to metabolic trauma caused by ectopic lipid deposition and lipotoxicity. At cellular level, lipids (mainly triglycerides and cholesteryl esters) are accumulated in cytoplasm as droplets varying in size (diameter 0.1–50 μm) and in the composition of a variety of coating proteins termed perilipins. In addition, lipid droplets are also associated with various small GTPases that, upon GDP-to-GTP conversion, are involved in membrane trafficking, tethering and fusion events. The heterogeneity in lipid and protein composition of lipid droplets may underlie functional diversity of cytosolic lipid droplets, although the functionality of these subcellular organelles remains largely unknown. Kiss and Nilsson, in their article titled “Rab proteins implicated in lipid storage and mobilization”^[2] have summarized recent experimental evidence for a potential role that several Rab GTPases play in the biogenesis, storage, and turnover of lipid droplets.

Intracellular degradation of proteins through the ubiquitin-proteasome system and/or autophagy is an important aspect of cellular homeostatic regulation.

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Apolipoprotein (apo) B, an obligatory protein constituent of triglyceride-rich lipoproteins (e.g. chylomicrons and VLDL), is synthesized constitutively and its metabolism is regulated mainly by the rate of intracellular degradation. McLeod et al. in their article titled “Apolipoprotein B100 quality control and the regulation of hepatic very low density lipoprotein secretion”^[3] have elegantly presented experimental evidence indicating that intracellular degradation of newly synthesized apoB may not be an unremarkable waste disposal event because of failed lipoprotein assembly or secretion. Rather, translation and subsequent lipid recruitment of apoB, under different metabolic conditions, are part of the quality control apparatus that is in intimate communication with cellular unfolded protein response (UPR) and endoplasmic reticulum stress mechanisms. Because of the central role that apoB plays in the development of premature atherosclerosis and in some cases non-alcoholic fatty liver diseases, defining the regulatory circuits that modulate apoB-lipid assembly and secretion is of major medical/clinical importance.

The intention of the Editorial Board of *Journal of Biomedical Research* in publishing these reviews is to disseminate timely current views and opinions of experts in the field, and to stimulate future investigations (i) in elucidating the cross-talk regulatory circuits between insulin and leptin signaling that are coordinately regulated by non-redundant, tissue/cell specific,

and compartmentalized protein tyrosine phosphatases, (ii) in unraveling the functional significance of the family of Rab GTPases bound to lipid droplets and the inter-relationship with their binding to other subcellular compartments such as endosome, lysosomes, and autophagolysosomes, and (iii) in deciphering the cellular/molecular mechanisms regulating the assembly/secretion of hepatic VLDL through post-translational degradation of apoB-100. It becomes increasingly clear that homeostatic regulation of lipid metabolism is achieved through on-off switches at multiple circuitry systems, including nutrient sensing, signaling (inter-organ, inter-cellular, as well as intracellular), biogenesis, storage, turnover, and secretion. Unraveling such complex metabolic networks and signaling networks is an achievable goal through the use of systems biology approaches, as oppose to traditional methodologies.

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