OVERVIEW AND INTRODUCTION: THEMATIC REVIEW SERIES ON INTESTINAL LIPID METABOLISM

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The last decade has seen extraordinary advances in our understanding of intestinal lipid metabolism, driven at least in part through attempts to mitigate the ongoing epidemic of obesity and metabolic disease (1). For example, weight loss strategies including gastric bypass surgery have brought to light unanticipated adaptations in metabolic homeostasis, including altered bile acid signaling and shifts in host-microbial ecology (2). As a result, our understanding of the role of the intestine in lipid metabolism now includes an expanded role in a range of homeostatic processes, including glucose metabolism, energy utilization, growth and inflammation to name but a few. Our thematic review will selectively cover several of these areas. In particular, we have solicited reviews that summarize a detailed elucidation of the pathways regulating the flux of complex lipids across the small intestinal enterocyte, including an emerging role in energy utilization and the role of circadian cues. We have also solicited reviews to provide a thorough understanding of the molecular, genetic and regulatory pathways involved in modulating intestinal bile acid transport and signaling and new insights into the role of nuclear hormone receptors in the intestine in maintenance of systemic lipid metabolism.

In the first article in our series, Eric Yen and his colleagues will review the role and regulation of enterocyte triglyceride synthesis, including the abundantly expressed genes acyl CoA:monoacylglycerol acyltransferase 2 (MGAT2) and acyl CoA:diacylglycerol acyltransferase 1 (ACAT1), whose functions have been examined in numerous model systems and have been shown to play crucial roles in the regulation of fat metabolism and energy utilization. There is heightened interest
also in the possibility that these pathways represent druggable targets for obesity and metabolic disorders (3).

In the second article, Mahmood Hussain and Xiaoyue Pan have summarized some of the recent developments in our understanding of the relevance of circadian rhythm to intestinal lipid metabolism. They summarize the role of innate intestinal Clock genes and outline the integration of central signals (via the suprachiasmatic nucleus) with environmental (i.e., feeding) cues (5). They address new developments in the circadian regulation of chylomicron assembly via transcriptional regulation of the gatekeeper gene microsomal triglyceride transfer protein (Mttp), including information gleaned from studies in Clock mutant mice. Hussain and Pan also provide intriguing new information regarding intestinal nocturnin as a regulator of intestinal lipid transport (6). In addition, these authors also review studies examining the diurnal and neuronal control of intestinal apolipoprotein A-IV.

In the third article, Emile Levy has undertaken a comprehensive summary of advances in understanding congenital disorders of intestinal lipid metabolism in humans. His summary includes a detailed overview of the features and underlying mechanisms contributing to phenotypes in familial hypobetalipoproteinemia and abetalipoproteinemia (7) as well as a review of Chylomicron Retention Disease (CRD) (8). Each of these disorders is linked to distinct genes which represent critical points in chylomicron assembly and secretion. Understanding the subtle
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Phenotypic distinctions associated with these rare autosomal disorders has greatly expanded insights into the molecular mechanisms regulating intestinal chylomicron maturation and the multivesicular transport pathway associated with the endoplasmic reticulum to Golgi transport. In addition, Levy expands on the observation that Sar1b defects (the causative allele implicated in CRD) impair intestinal chylomicron but not hepatic very low density lipoprotein secretion, which implies that there are tissue-specific differences in triglyceride rich lipoprotein secretion that await further resolution. Levy further provides information on the loss of function phenotypes associated with PCSK9 variants and ANGPTL3 defects.

In the fourth article, Paul Dawson and Saul Karpen summarize the latest understanding of intestinal bile acid transport physiology. Their review includes a comprehensive examination of the regional distribution and function of apical and basolateral intestinal bile acid transporters. In addition, they summarize the role of intestinal bile acid transport in the context of regulatory mechanisms and pathways (including FXR-FGF15/19) that regulate enterohepatic bile acid recycling and conservation and in turn regulate cholesterol utilization for bile acid synthesis. They also review the role of gut microbial bile acid metabolism and signaling through G-coupled receptors. This is a timely overview in light of the expanding role of host-microbial interactions and FXR signaling, which have been implicated in growth, inflammation and metabolic homeostasis, particularly after gastric bypass surgery (9).
In the fifth article, Antonio Moschetta and colleagues review the role of lipid-sensing nuclear hormone receptors in the control of both intestinal cholesterol flux and also in the context of high density lipoprotein production. They review the distribution and function of nuclear receptors throughout the intestinal tract and summarize findings pointing to their role in regulating cholesterol flux, both uptake and excretion. Their review also encompasses discussion of the pathways regulating reverse cholesterol transport and how these relate to our understanding of trans-intestinal cholesterol flux (TICE) a newly described mechanism (still poorly understood) for mediating cholesterol excretion (beyond biliary secretion) (10).

In the sixth and final article, Patrick Tso and colleagues summarize the current understanding of the physiological roles and functions of apolipoprotein A-IV (apoA-IV). Work performed several decades ago noted that apoA-IV is synthesized within enterocytes of the small intestine where it is associated with chylomicrons and undergoes secretion into the lymphatic compartment. Over the years, various functions have been assigned to apoA-IV including anti-oxidative and anti-inflammatory properties as well as a satiety factor. Tso and colleagues summarize work showing how apoA-IV promotes reverse cholesterol transport and also how apoA-IV itself may modulate intestinal lipid absorption. In addition, they summarize exciting new work showing that apoA-IV promotes insulin secretion and decreases hepatic gluconeogenesis, suggesting an expanded role in metabolic homeostasis (11).
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Taken together these review articles provide a timely resource for investigators interested in understanding a range of developments in our understanding of intestinal lipid metabolism. We hope that this series will stimulate interest in the field of intestinal lipid metabolism and its expanding impact on a range of homeostatic processes. Our field is undergoing a seismic shift, driven particularly by an emerging understanding of signaling molecules that are influenced by the host microbiome and which are likely to be players in metabolic disease as well as growth, development, inflammation and cancer.
REFERENCES


Figure legend. Summary overview figure outlining the central elements of this upcoming Thematic Review Series. Central panel shows schematic diagram of small intestinal enterocyte with mitochondria, Golgi and Endoplasmic reticulum. The expanded bilayer to the right of the enterocyte represents the topology of triglyceride resynthesizing enzymes and the process of mobilizing complex lipid for chylomicron assembly. Yellow spheres are lipid droplets. A progressively enlarging prechylomicron is shown at the lower left corner of the enterocyte and the mature chylomicron particle shown along with a spherical high density lipoprotein particle (not to scale). Apolipoproteins B48, A-I and A-IV are in the surface. The membrane bilayer above the enterocyte represents the ileal bile acid transporter (ASBT). The modular image of duplexed factors binding to DNA represent the role of nuclear hormone receptors in intestinal HDL production. The image of the clock above the Michelangelo figure represents the concept of diurnal rhythms in intestinal lipid metabolism.
Figure