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**The multiple fuels of BAT thermogenesis**

**pp. 4–11**
In this mini-review, Dr. Hankir explores the mechanisms by which brown adipose tissue (BAT) regulates thermogenesis and how multiple forms of thermogenesis is fueled in response to various triggers. These studies show how fuels such as glucose and lipids, in conjunction with BAT, can be used to treat ailments such as hyperglycemia and hyperlipidemia. Furthermore, a model presented here shows how both diet-acquired fatty acids and glucose as well as BAT derived fatty acids, and, acylcarnitine contribute to BAT activation and thermogenesis when responding to cold (Fig. 1).

**Autophagy, gene expression, and glucometabolic status**

**pp. 12–19**
Adipose tissue (AT) autophagy has recently been linked to lipid metabolism, having already been associated with human obesity and other metabolic disorders. In many studies, autophagy markers in AT have been upregulated in obese mice and humans. This research paper by Xu et al. examines gene expression (both autophagy-related and classical lipolysis) in the abdominal subcutaneous AT of high BMI subjects compared to lean glucose tolerant subjects to shed light on links between AT autophagy and lipolysis (Fig. 2).

**Ovariectomy, moderate exercise and white adipose tissue inflammation**

**pp. 20–34**
Previous models have shown that ovariectomized (OVX) rats gain both weight in the form of white adipose

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**Figure 1.** Plasticity of brown adipocyte substrate utilization for cold-induced thermogenesis. Hankir p. 8.

**Figure 2.** mRNA expression of autophagy and classical lipolysis markers in human subcutaneous AT of obese (black bars) and lean (white bars) subjects. Xu et al. p. 13.
tissue (WAT) rapidly as well as insulin resistance (IR), and this gain is amplified when a high fat diet is present. However, rats predisposed for high aerobic fitness (HCR) are protected from this. It is known that physical activity has been shown to reduce WAT inflammation in rodents, and in this research paper by Zidon et al., wheel running was used to introduce physical activity in both OVX HCR rats and low aerobic fitness (LCR) rats. This exercise was enough to lower WAT inflammation in previously sedentary LCR rats, however it had an opposite effect that increased adiposity and inflammation in OVX HCR rats.

Untangling adipose inflammation, insulin resistance and vascular endothelial dysfunction

While rodent models have shown that induced ovarian hormone deficiency contributes to insulin resistance and cardiovascular disease risk via increases in adipose tissue inflammation and adiposity, whether this same relationship exists in a larger animal model is unclear. Jurrissen et al. use female Yucatan mini-swine in this research paper to see if an ovariectomy results in similar adiposity and AT inflammation increases. Although OVX pigs did not show an increase in body mass, AT inflammation, or glucose homeostasis, they did show an increase in triglyceride:HDL ratio as well as endothelial dysfunction (Fig. 3).

Adipose derived FGF2 in malignant transformation

Having previously shown that the number of ultraviolet radiation-initiated, high-fat diet-promoted skin cancers can be significantly reduced via the removal of visceral adipose tissue, authors Chakraborty, Benham and Bernard focus on the malignant transformation of epithelial cells. Their new study shows that malignant transformation in fibroblast growth factor receptor 1 expressing epithelial tissues can be stimulated by the fibroblast growth factor-2 (FGF2) released from visceral adipose tissue. This commentary provides insights from this study as well as new data on the key role that FGF2 plays in adiposity-associated tumorigenesis (Fig. 4).

Understanding our gut

The food we eat and how diet can impact human disease has long been a focus of interest. However, authors Schugar, Willard, Wang, and Brown note that our understanding of the microbes in our gut who share our body and their impact on obesity and metabolic disease is lacking. In this commentary, the authors dive into recent work identifying the bacterial co-metabolite trimethylamine-N-oxide (TMAO) as a suppressor of white adipose tissue beiging, as well as the link between the TMAO pathway and numerous obesity-related diseases and disorders (Fig. 5).

A new marker in Adiponectin/leptin ratio

Due to the correlation between an increase in leptin concentration and a decrease of adiponectin in the blood with regards to obesity and the metabolic syndrome (MS), the ratio between adiponectin and leptin can be seen as an adipose tissue dysfunction marker. Authors Frünbeck, Catalán, Rodríguez, and Gómez-Ambrosi discuss how the usage of this marker may be a better gauge for identifying present metabolic risk factors, as well as some types of cancer. In this commentary, the authors
present new ways to measure obesity and MS associated cardiometabolic risk through new cutoffs of s adiponectin/leptin ratio, and, approaches to mitigate metabolic risk by increasing this ratio.

Regulating ER stress and attacking obesity through GRP78

pp. 63–66

Understanding how the central nervous system is linked to energy expenditure and obesity has become a new avenue for therapeutic research. The regulator of endoplasmic reticulum (ER) stress known as glucose related protein 78 (GRP78), when overexpressed in the ventromedial nucleus of the hypothalamus, can result in weight loss as well as improved insulin and leptin sensitivity via released ER stress. In this commentary, authors Contreras, Fondevila, and López weigh in on how hypothalamic GRP78 can impact energy balance, BAT thermogenesis, WAT browning, and how it may serve as a novel target against obesity.

Figure 5. Working model by which the TMAO pathway promotes obesity and cardiometabolic diseases. Schugar et. al., p. 50.