

regulating UCP1 and mitophagy. These data indicate that the commonly used pesticide chlorpyrifos, at doses found within the food supply, suppresses the activation of brown adipose tissue, suggesting that its use may contribute to the obesity epidemic.

## Adipose Tissue, Appetite, and Obesity NOVEL MECHANISMS CONTROLLING ADIPOSE TISSUE PHYSIOLOGY AND ENERGY BALANCE

### *TNF Alpha-Induced SOX2 Expression Promotes Hepatic Steatois in Diet-Induced Obesity Model*

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Diet-induced obesity can cause metabolic or inflammatory damage on liver. Nonalcoholic fatty liver disease (NAFLD) begins with the fat accumulation in hepatocyte, but can lead to hepatocellular carcinoma (HCC). Sex-determining region Y-box 2 (SOX2) is a critical transcription factor involving regeneration and pluripotency. The expression level of Sox2 is correlated with progression of HCC, and anti-inflammatory effects of Sox2 in mesenchymal stem cells have been found. However, the expression of Sox2 by inflammatory cytokines in hepatocyte in NAFLD or the role of SOX2 in fat accumulation has been rarely reported. Here, we found that high-fat diet feeding, with or without high fructose in drinking water, significantly upregulated SOX2 in the livers of mice. In vitro, treatment with free fatty acids (FFAs) and fructose increased SOX2 expression in FL83B cells compared with the vehicle-treated group. Furthermore, overexpression or knockdown of SOX2 in FL83B cells promoted or suppressed, respectively, triglyceride synthesis and lipid accumulation after FFAs stimulation. The expression levels of several lipogenesis-related molecules were found to be altered by SOX2 expression. In addition, among several cytokines, only the treatment of tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) increased the SOX2 expression compared with the vehicle-treated control. Further, upregulation of (TNF $\alpha$ ) by FFA/fructose was observed, and TNF $\alpha$  and FFA/fructose induced SOX2 expression was abolished by pretreatment of a TNF $\alpha$  inhibitor. Collectively, our findings suggest that TNF $\alpha$ -SOX2 signaling pathway in hepatocyte may be one of targets for early prevention of the development of NAFLD.

## Adipose Tissue, Appetite, and Obesity NOVEL MECHANISMS CONTROLLING ADIPOSE TISSUE PHYSIOLOGY AND ENERGY BALANCE

### *Unraveling Secretory Mechanisms that Control Pentraxin 3 Secretion in Adipocytes During Inflammation*

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As a soluble pattern recognition receptor, Pentraxin 3 (PTX3) plays an important role in innate immunity and obesity-associated metabolic inflammation. PTX3 is abundantly

expressed and secreted in adipocytes in response to lipopolysaccharide (LPS) stimulation. Appropriate regulation of PTX3 secretion is critical for maintaining inflammatory homeostasis. This study aims to unravel the mechanisms that control PTX3 secretion in adipocytes during LPS-induced inflammation. Upon 6h treatment of LPS, PTX3 expression and secretion were significantly induced in 3T3-L1 and stromal-vascular (SV) differentiated adipocytes, but to a lesser extent in SV cells or 3T3-L1 fibroblasts. However, LPS does not significantly stimulate PTX3 expression and secretion in macrophages. Using chemical inhibitors of conventional and unconventional protein secretion, we explored the mechanisms for controlling LPS-stimulated PTX3 secretion. 3T3-L1 adipocytes were treated with LPS for 6h in the presence or absence of various inhibitors blocking protein secretion from the Golgi complex (Monensin and Brefeldin A), mitochondrial oxidation (carbonyl cyanide 3-chlorophenylhydrazone [CCCP]), autophagy-lysosome (chloroquine and 3-methyladenine) and inflammasome (Bay 11-7082 and wedelolactone) activation, or exosome synthesis and trafficking (GW4869, manumycin A, calpeptin, and Y-27632). There were no significant effects of all inhibitors except for Monensin, Brefeldin A, and CCCP on intracellular and secreted levels of PTX3 in adipocytes. We found that Monensin and Brefeldin A significantly blocked LPS-stimulated PTX3 secretion, resulting in cellular PTX3 accumulation in adipocytes. Disrupting mitochondrial membrane potential by CCCP caused the reduction in PTX3 secretion from adipocytes. Additionally, we detected PTX3 in exosomes isolated from LPS-treated adipocytes. Inhibiting exosome synthesis by Manumycin A attenuated LPS-stimulated PTX3 secretion in both adipocyte culture media and isolated exosomes but not in the non-exosomal fraction of media, suggesting the involvement of the exosomal pathway in PTX3 secretion. However, the levels of exosomal PTX3 were significantly lower than that of the non-exosomal PTX3, and only 4.3% of secreted PTX3 was detected in the exosomal fraction of culture media. Inhibiting the Golgi complex pathway blocked both the exosomal and non-exosomal secretion of PTX3 in adipocytes. After further fractionation of isolated crude exosomes by the iodixanol density gradient centrifugation, we showed that the majority of PTX3 was found in the non-extracellular vesicular (EV) fractions; only a small portion of secreted PTX3 overlapped with the exosomal marker CD63 in the small EV fractions. We conclude that PTX3 is secreted mainly through the conventional protein secretion pathway and minimally through the exosomal or EV pathway in response to LPS stimulation.

## Adipose Tissue, Appetite, and Obesity THE RELATIONSHIP BETWEEN COVID-19 AND ENDOCRINOLOGY

### *Antiandrogens Target TMPRSS2 and Reduce SARS- CoV-2 Virus Entry in Lung Cells*

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