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 (TNFα) increased the SOX2 expression compared with the vehicle-treated control. Further, upregulation of (TNFα) by FFA/fructose was observed, and TNFα and FFA/fructose induced SOX2 expression was abolished by pretreatment of a TNFα inhibitor. Collectively, our findings suggest that TNFα-SOX2 signaling pathway in hepatocyte may be one of targets for early prevention of the development of NAFLD.

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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, LPSdoes 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 cultural 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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The SARS-CoV-2 coronavirus is the cause of the COVID-19 pandemic. Entry of the virus into host cells, most destructively lung cells, requires two host cell surface proteins, ACE2 and TMPRSS2, downregulation of which is thus a potential therapeutic approach for COVID-19. Both of these cell surface proteins are steroid regulated: TMPRSS2 is a well-characterised androgen-regulated target in prostate cancer. Analysis of sequencing data shows co-expression of the androgen receptor (AR) and TMPRSS2 in key human lung cell types that are targeted by SARS- CoV-2. We show that treatment with antiandrogens such as enzalutamide (a well-tolerated drug widely used in advanced prostate cancer) significantly reduces TMPRSS2 levels in human lung cells and in vivo in mouse lung. We demonstrate that AR binding in the region of the TMPRSS2 gene differs between lung and prostate, identifying distinct regulatory regions. Together, the data and evidence presented supports clinical trials to assess the efficacy of antiandrogens as a treatment option for COVID-19.

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

Early Follow-up of Atypical Thyroiditis Induced by SARS-CoV-2

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Background: In Spring 2020 the severe acute respiratory syndrome coronavirus 2 pandemic disease (Covid-19) badly affected Northern Italy. We have described for the first time the occurrence of thyrotoxicosis due to atypical subacute thyroiditis in 15% of patients hospitalised for Covid-19 pneumonia, compared with only 1% among patients hospitalised in the same wards during Spring 2019, thus before the Covid-19 pandemic. The whole group of Covid-19 patients also had median serum TSH concentrations significantly lower compared with the control group. The atypical thyroiditis induced by Covid-19 is not associated with neck pain, affects more men than women and especially those severely ill, thus coexists with non-thyroidal illness syndrome. Subacute thyroiditis is classically followed by subsequent occurrence of permanent thyroid dysfunction and autoimmunity, thus we have started a systematic follow-up program of these patients.
Methods: Longitudinal follow-up study of survived Covid-19 patients without previous known history of thyroid disorders and/or medications, assessing serum thyroid function and autoantibodies, C reactive protein (CRP), full blood count (FBC) and thyroid ultrasound (US) every 3 months. Patients showing baseline (at hospitalisation for Covid-19) thyroid dysfunction and/or focal hypoechoic areas suggestive for subacute thyroiditis at US performed 3 months post-infection, also underwent thyroid ^{99m}Tc or I^{123}uptake.
Results: To date, 53 patients have been included in the follow-up study. At 3 months post-infection, all of them presented with increased median (IQR) serum TSH concentrations compared with baseline: 1.3 (0.9–2.0) mIU/L versus 0.9 (0.5–1.8) mIU/L (p=0.0001). Similarly, serum concentrations of free-thyroxine, free-triiodothyronine, CRP and FBC had normalised compared with baseline. All patients had negative autoantibodies to TSH receptor; autoantibodies to thyroglobulin and to thyroid peroxidase were positive in 6/53 (11%) and 5/53 (9%) of patients, respectively. The thyroid US showed the presence of focal hypoechoic areas of thyroiditis in 16/51 (32%) patients, with thyroid uptake normal in 6/16 (37%), focally reduced in 8/16 (50%) and diffusely reduced in 2/16 (12%).
Conclusions: At 3 months after Covid-19 disease all patients had a normalised thyroid function, however imaging findings suggestive for subacute thyroiditis were still present in about one third of cases. The thyroid dysfunction induced by Covid-19 seems not mediated by autoimmunity. It is important to continue to follow these patients since they might develop thyroid dysfunction during the following months.

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THE RELATIONSHIP BETWEEN COVID-19 AND ENDOCRINOLOGY

Obesity Is Associated With Intensive Care Use and Duration of ICU Stay but Not Mortality Among 3246 Patients Hospitalized With COVID-19

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Obesity is associated with increased severity of viral illnesses, but its impact on outcomes in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is yet to be elucidated. We sought to determine the association of obesity and other clinical factors with outcomes among patients hospitalized for severe coronavirus disease (COVID-19). This study included patients hospitalized between March 1, 2020 and September 17, 2020 in a 5-hospital health care system in Northeast United States, who had a positive RT-PCR assay of nasopharyngeal swabs for SARS-CoV-2 performed during hospitalization. Body mass index (BMI) was calculated using admission weight and height, and the WHO classification was used to define obesity. Both bivariate and multivariate logistic regression analyses were performed to determine the association of obesity and other clinical parameters with mortality (defined as in-hospital death or transition to hospice care) and intensive care use (defined by transfer to intensive care unit [ICU]). Multivariate model was adjusted for demographics and 8 pertinent comorbidities. Among 3246 patients hospitalized with COVID-19, median age was 65 years (interquartile range, 51–78), 49.9% were female, 30.5% overweight, and 43.2% had obesity (20.8%,