SL08 Anatomical, Functional and Molecular Adipose Tissue-Based Sub-Typing of Obesity and Fatty Liver Disease

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With the growing prevalence of obesity, it is increasingly becoming clear that we currently define obesity at very low resolution: Obese patients (officially still defined based on BMI) exhibit a wide range of obesity-related health risks. Thus, sub-typing/risk-stratifying obesity is greatly needed, both for providing better precision care, for developing novel therapies, and for increasing our etiologic and mechanistic understanding of obesity-associated co-morbidities. This presentation will summarize the work of various groups, including ours, which seeks to examine if adipose tissue features – distribution, function, and molecular signatures – can in fact assist in elucidating obese sub-types with different health risks and/or response to therapy.

Adipocyte size and adipose tissue collagen deposition have been linked to obesity-associated diabetes, and shown to predict response to bariatric surgery. Another prominent feature is adipose tissue inflammation. We demonstrated that adipose tissue foam cells in visceral fat associate, and can cause, insulin resistance and systemic inflammation *(JCEM 98: 1173, 2013)*. Clinically, adipose tissue foam cells can be estimated by a higher percent of non-classical (i.e., $CD14^{dim}/CD16^{high}$) circulating monocytes, particularly in men *(PLoS One 11: e0159350, 2016)*. Molecularly, we identified an adipose tissue stress network characterized by adipocyte overexpression of the cell-cycle regulator E2F1. This transcription factor, when highly expressed, binds to promoters of genes, thereby activating a MAP kinase signaling cascade (ASK1(MAP3K5)→MKK4→ JNK/p38MAPK)*(Mol Metab 6: 725, 2017)*, and autophagy *(Autophagy 11: 2074, 2015)*. Each of these pathways could be linked to low adiponectin secretion *(Int J Obes 40:912, 2016)*, a feature of dysfunctional adipose tissue.

Finally, the "(visceral)-fat - liver axis" is central in the pathogenesis of obesity-associated cardio-metabolic risk. Indeed, the aforementioned adipose tissue stress network appears to induce hepatocyte lipid accumulation by impairing adiponectin production, which can be pharmacologically prevented *in-vitro (Int J Obes 40:912, 2016)*. Results of a recent clinical trial indicate that many beneficial effects of life-style interventions aimed at targeting visceral fat are mediated by diminishing liver fat content *(Circulation, In Press)*. Obesity reversal studies in mice demonstrate that adipose tissue supports this change, despite seeming residual inflammation *(J Endocrinol 233: 293, 2017)*.

In summary, this presentation will explore the notion that obesity may be sub-phenotyped by considering adipose adaptation to obesity and to weight loss. Moreover, it will propose novel avenues to address obesity-associated metabolic dysfunction by improving non-alcoholic fatty liver disease.