Obesity is a risk factor for increased COVID-19 severity and morbidity: hypoxic adipose responses and increased inflammation in bronchial pulmonary cells

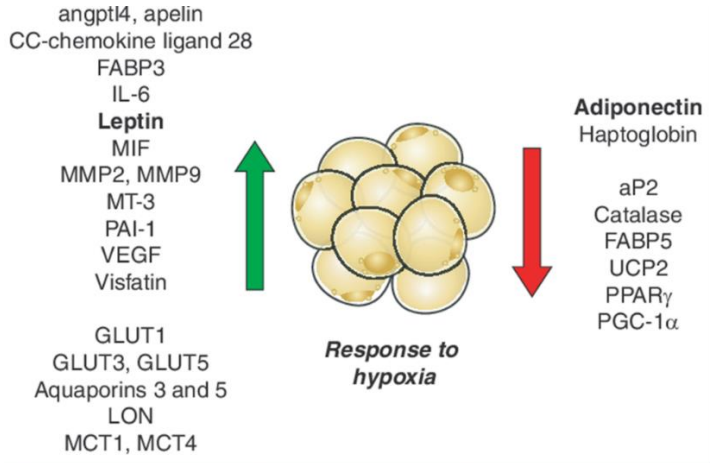
Background

Being overweight and obesity are associated with various diseases, including cardiovascular diseases, metabolic disorders, renal and biliary diseases, and certain types of cancer. The relationship between obesity and pulmonary dysfunction is becoming increasingly clear. Researchers have shown for the first time that fatty tissue accumulates in the airway walls, particularly in people who are overweight or obese (Elliot *et al*., 2019). The direct action of adipose tissue on pulmonary dysfunction might be related to a decrease in the luminal diameter of the airways.

COVID-19 is the new out-breaking disease, characterised by pneumonia and acute respiratory distress syndrome (ARDS). Many people infected with SARS-CoV-2 show no symptoms or display flu-like symptoms (Chen *et al*., 2020; Zhang *et al*., 2020). However, in overweight and obese people, there is a strong correlation between the body mass index (BMI) and the severity, the complications, and the mortality risk of SARS-CoV-2 viral infections (Goumenou *et al*., 2020). This correlation was previously pointed out for the previous corona-viruses, such as the severe acute respiratory syndrome (SARS) or the Middle East respiratory syndrome (MERS) (Moser *et al*., 2019; Muniyappa *et al*., 2020). The COVID-19 infection combines “anaemic hypoxia” (low haemoglobin concentration), with the low haemoglobin oxygen saturation. This will result in oxygen deprivation in lung tissues generating a decrease in oxygen supply to other organs such as the brain, liver, kidney and white adipose tissue (WAT).

Research proposal

In obese mice WAT, hypoxia induces a dysregulation in adipocyte functions, whether in obese patient adipose tissue, the low oxygen supply is still unclear. *In vitro*, both murine and human adipocytes exhibit extensive functional changes in response to hypoxia, which alters the expression of up to 1,300 genes. These include genes encoding adipokines such as leptin, interleukin 6 (IL-6), vascular endothelial growth factor (VEGF), and matrix metalloproteinase-2 (MMP-2). Hypoxia also inhibits the expression of genes linked to oxidative metabolism while stimulating the expression of genes associated with glycolysis. Glucose uptake and lactate release by adipocytes are both stimulated by hypoxia (Pérez de Heredia *et al*., 2010; Trayhurn, 2014).



Effects of hypoxia on the expression of key genes in human adipocytes (↑increased,↓decreased expression in response to low O2 tension). *Trayhurn P. (2014). Annu. Rev. Nutr. 2014. 34:207–36*

To understand the underlying mechanism between white adipose tissue expansion, hypoxia and the severity related to COVID-19 infection in overweight and obesity status, our project aims to investigate the cross talk between both subcutaneous and visceral human adipocytes (VWA & SCWA), and human bronchial epithelial cells (HBEpC) under normoxic and hypoxic conditions.

- VWA, SCWA and HBpC will be maintained for short and long terms under different PO_2 conditions (1%, 5%, 10% and 20%). The released cytokines and chemokines in response to the different culture conditions, will be measured using a multiplex technique. The up-regulation and down-regulation of target genes will be evaluated in the different cell populations.

- To understand the effect of systemic inflammation in adipose tissue on lung tissue, the HBpC will be incubated in the presence or absence of adipocytes condition media (ACM) collected from normoxic and hypoxic SCWA and VWA cell cultures.

- To investigate the cross talk between both tissues, cell co-cultures of VWA and HBpC will be carried out under normoxic and hypoxic conditions. Oxidative stress, the changes in pro-inflammatory and vascular injury markers levels will be evaluated.

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