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## Site-specific mitochondrial ROS production underlies alterations in liver glucose homeostasis in obesity

Mitochondrial superoxide and $H_2O_2$, collectively referred to as mitochondrial reactive oxygen species (mROS), play a key role in the development of obesity-associated metabolic disorders, such as insulin resistance, in different tissues. Despite its pathophysiological relevance, the mechanism by which mROS is regulated to impair glucose and lipid homeostasis is not fully explored. mROS is not a single process; eleven sites in the mitochondrial electron transport chain (ETC) and matrix can leak electrons to oxygen generating superoxide/$H_2O_2$. However, it is unclear whether, in obesity, mROS production is generally increased or if it is altered at specific sites. Here we found that in obese livers, the flux through coenzyme Q synthesis is compromised which is associated with an increase in the COQH2/COQ ratio and high ROS production from complex I at site $I_Q$ via reverse electron transport (RET). Targeting the ectopic expression of *Ciona intestinalis* alternative oxidase (Aox) to the liver of obese mice improves glucose and lipid homeostasis. On the other hand, promoting mROS specifically at complex I/site $I_Q$ in lean mice deteriorates glucose homeostasis by decreasing mitochondrial NADH:$NAD^+$ ratio and promoting liver glucose production and inflammatory pathways. Taken together, our findings show that increased mROS in obesity is a regulated process and identified site $I_Q$ via RET as the main source of excess mROS in the liver in obesity removing a major roadblock to the development of therapies targeting superoxide/$H_2O_2$ in the mitochondria to improve metabolic function.