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EDITORIAL

NO to Lysosomes: A Signal for Insulin Resistance in Obesity

The activity of inducible-nitric oxide synthase (iNOS) is subject to spatiotemporal regulation, which is central to iNOS action in human disease. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Qian et al[1] show that obesity stimulates lysosomal iNOS localization, which generates nitric oxide (NO) from lysosomal arginine stores and impairs lysosome function. Lysosomal NO generation drives mammalian target of rapamycin (mTOR) activation with suppression of transcription factor EB (TFEB) activity.

TFEB (along with the other members of Microphthalmia family (MiT/TFE) of transcription factors) is a master regulator of the autophagy–lysosome machinery in mammals, and its transcriptional activity is suppressed by mTOR-mediated phosphorylation and sequestration in the cytoplasm. The current studies implicate NO-induced TFEB suppression as a novel mechanistic step in autophagy–lysosome pathway impairment in the liver during overnutrition. By using state-of-the art biochemical approaches and imaging-based tools to assess lysosomal NO levels, Qian et al[1] discovered that mice lacking iNOS are protected from both lysosomal NO overload in hepatocytes and insulin resistance secondary to diet-induced obesity. These studies build on their prior work, wherein this group discovered that increased S-nitrosylation of lysosomal proteins in obese livers triggers lysosomal enzymatic dysfunction.[2] This was coupled with reduced expression of the enzyme, S-nitrosoglutathione reductase, a major protein denitrosylase that transfers NO groups from S-nitrosylated proteins to glutathione. The current studies elegantly show that in the setting of diet-induced obesity, iNOS-mediated TFEB inactivation suppresses hepatic autophagy. Genetic ablation of iNOS reduces liver fat content, and short hairpin RNA–mediated iNOS knockdown restores insulin signaling via activating endogenous TFEB in a mouse model of diet-induced obesity. Indeed, in light of prior studies showing that iNOS is degraded in lysosomes,[3] NO-induced lysosomal dysfunction also may be a feed-forward mechanism to drive further NO generation within lysosomes in obese livers by impairing iNOS degradation. Taken together, these data provide compelling evidence that NO generation in lysosomes drives hepatic insulin resistance in obesity, and underscores the need for exploration of therapeutic targets in this pathway to counter disease pathogenesis.

In the context of the broader literature, there appears to be significant benefit to augmenting TFEB activity in metabolic disease and conditions of autophagic impairment. For example, work in our laboratory has uncovered that intermittent fasting, a sustainable strategy for pulsed activation of TFEB and the autophagy–lysosome pathway, can restore glucose homeostasis in high-fat–fed mice[4] and prevent mortality in mice that develop heart failure owing to expression of a mutant form of αB-crystallin.[5] In addition, TFEB activation using genetic approaches has shown efficacy in clearing protein aggregates in neurodegenerative diseases and in atherosclerosis. Indeed, small-molecule activators of TFEB have been developed that mechanistically drive its activation via suppressing mTOR activity (via suppressing its tonic phosphorylation of TFEB) or targeting calcium release from various intracellular stores to stimulate calcineurin-mediated dephosphorylation of TFEB.[6] These small molecules were effective in ameliorating the metabolic syndrome to confer hepatic protection in murine models of fatty liver. In this light, it is important to consider that approaches to activate TFEB could be complicated by its involvement in cancer, immune activation, the DNA damage response, and the potential for excessive stimulation of autophagy to drive cell death. Therefore, clinical development of small molecules targeting TFEB should consider cell-type specificity and the timing of therapy, with a particular focus on time-limited or pulsed TFEB activation.

The current study begs the question: could there be a role for iNOS inhibition in restoring TFEB activity to physiological levels under metabolic stress and inflammation? Studies to determine if iNOS regulates the activity of the MiT/TFE family of transcription factors in other disease states such as sepsis, atherosclerosis, and obstructive airway disease (where iNOS activation is implicated in pathogenesis) could provide valuable insights in this regard. However, the extant experience with iNOS inhibitors is a cautionary tale for clinical translation of basic findings. The failure of multiple clinical trials of iNOS inhibitors in septic shock, asthma, and cardiogenic shock may have been owing in part to the lack of selectivity for the target and potential inhibition of endothelial nitric oxide synthase. With the development of precisely targeted therapeutics, careful studies such as the present one by Qian et al[1] may prompt renewed interest in iNOS inhibition as a novel approach to reactivate autophagy and TFEB in obesity to counter insulin resistance. A significant caveat of the current study is that the in vivo observations in the germline iNOS null model likely involve a complex interplay between effects in hepatocytes, inflammatory cells, and other liver-resident cell types. Dissecting these mechanisms will require targeted approaches to understand the cell-type specific role of lysosomal iNOS under metabolic stress. Notwithstanding these limitations, the current observations lay the foundation for exploring the efficacy of targeting lysosomal nitrosative stress for enhancing lysosome function as a therapy in obesity.

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Conflicts of interest
The authors disclose no conflicts.

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