Accelerated oxidative renal damage in high fat diet fed heterozygous sirtuin1 mice

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Mitochondria are the main source of energy for renal metabolism and function (Xiao et al Redox Biology 11, 297-311, 2017). Recent studies have demonstrated the crucial role of mitochondria in obesity, diabetes and related metabolic diseases (Stacchiotti et al PlosOne 9, e111141, 2014; Duann and Lin Adv Exp Med Biol 982, 529-551, 2017). Sirtuin 1 (silent mating type information regulation 2 homolog 1), a homolog of the life-extending gene sir 2 in mammals, sustains mitochondria health through the deacetylation of peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1 alpha) and the direct regulation of mitochondrial DNA and replication (Hasegawa et al J Biol Chem 285, 13045-13056, 2010). In this microscopic and ultrastructural study we analyzed the renal effects of an obesogenic high fat diet (58.4 % lard) (HF) (Envigo TD 03584) in heterozygous sirtuin1 mice (HET) compared to C57BL/6J mice (WT), challenged with the same diet for 16 weeks from 12 to 28 weeks of age. Major aim was to best characterize mitochondria feature in glomerulus and cortical proximal tubules, which strictly rely on oxidative metabolism.

Glucose intolerance developed together with glomerular and renal hypertrophy in both WT HF and HET HF mice versus standard rodent diet (SD) (Safe A04 8.4 % fat) fed control groups. However, in HET HF mice kidney, lipid peroxidation assessed by 4 hydroxy-2-nonenal (4HNE) immunostaining, fibrosis by collagen IV expression and trichrome Masson, PAS stainings, apoptosis were exacerbated. Ultrastructural analysis revealed glomerular podocytes foot effacement, basal membrane thickening and mesangial matrix overproduction. Moreover, in cortical proximal tubules myelinic figures and abnormal mitophagy, even if sometimes present in HET SD mice, prevailed in HET HF over WT HF mice. These findings were corroborated by intense tubular p62/sequestosome 1 (SQSTM1) and sterol regulatory element-binding protein 1 (SREBP1c) expressions and the greater percentage of damaged round or donut-like mitochondria, devoid of regular cristae, in obese HET mice (45% vs 30% WT HF vs 10% WT SD). In conclusion, HET HF mice represent an intriguing translational model to best address the role of oxidative metabolism in crucial organs like kidney.