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Thyroid hormone regulation of autophagy and metabolism

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Statement of the Problem: Thyroid hormone (TH) plays a key role of metabolism and its dysfunction may be involved in non-alcoholic fatty liver disease (NAFLD). We previously showed that TH induces autophagy in the liver to promote the degradation and hydrolysis of triglycerides stored in fat droplets into free fatty acids (Lipophagy). Metabolomics analysis showed that TH also stimulated fatty acid β-oxidation.

Findings: TH increased mitophagy in hepatic cells *in vivo* that was associated with increased oxidative phosphorylation. This was evident from co-localization of autophagy/autolysosomal markers and mitochondria using confocal and electron microscopy. Furthermore, we found that T3 induced a concomitant increase in ROS that was crucial for TH-induced mitophagy through the AMPK/ULK1 pathway. Additionally, we showed that T3 is a potent inducer of mitochondrial biosynthesis and utilizes that activation of another nuclear hormone receptor ERRa to mediate many of its actions.

Conclusion & Significance: Our results describe a novel co-ordinated mechanism of TH-induced fatty acid β-oxidation that is dependent upon mitochondrial turnover. These findings suggest that low dose Levothyroxine or thyroid hormone analogs may be beneficial for patients with hepatosteatosis related to NAFLD and obesity.

Biography

Paul M Yen is a Professor at Duke-NUS Graduate Medical School in Singapore and Head of the Laboratory of Hormonal Regulation in the Cardiovascular and Metabolic Disorders Program. He has obtained his MD from Johns Hopkins, completed his Residency in Internal Medicine at University of Chicago and his Endocrinology Fellowship at NIH. Prior to Duke-NUS, he has served on the Faculty at Johns Hopkins, Harvard and as a Section Chief at NIDDK, NIH. He has served on the Editorial Boards of *Endocrinology, Molecular Endocrinology* and *Thyroid*. His current research interests are hormonal regulation of hepatic autophagy and lipid metabolism in non-alcoholic fatty liver disease as well as epigenetic regulation of metabolic genes by thyroid hormone.

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