INVESTIGATION OF DIET-INDUCED ALTERATIONS IN MITOCHONDRIAL DNA AND METABOLISM IN BROWN ADIPOSE TISSUE: IMPLICATIONS IN OBESITY-RELATED DIABETES

PhD Student: Mehrdad Norouzi

Supervisor: Prof. Katia Aquilano/*Co-supervisor*: Dr. Daniele Lettieri Barbato

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The measure of all exposures of an individual in a lifetime and how those exposures relate to health is called "exposome". Diet is an environmental exposure factor that can have a lifelong impact on our health. Moreover, extra calorie intake leads to fat deposition, expansion of white adipose tissue, and obesity. Importantly, obesity is the major risk factor for lifestyle-related metabolic disorders such as type 2 diabetes (T2D), hypertension, hyperlipidemia, coronary heart disease, and even cancer. Brown adipose tissue (BAT), as a mitochondria-rich tissue with high oxidative efficiency, can have thermogenic function thanks to the UCP1 activity. Indeed, UCP1 increments the conductivity of the inner membrane of mitochondria to make BAT mitochondria generate heat rather than ATP. In fact, BAT inactivation in adult humans is considered a contributing factor in the development of obesity-related T2D. Mitochondria contain their own circular DNA encoding for 37 genes among which 13 genes code for electron transport chain (ETC) proteins that are vital for cellular metabolism. Although many studies have been carried out about the structure and function of mitochondria, the molecular mechanisms that clarify the regulation of mtDNA expression are not so clear yet. However, it is now evident that mitochondria can epigenetically alter mtDNA expression through their machinery. On the other hand, although it is well known that nutrients can greatly impact nuclear DNA (nDNA) expression, there is not much evidence regarding their influence on mtDNA expression. Consequently, characterizing the alterations of mtDNA expression and mitochondrial metabolism occurring in BAT using a mouse model of obesity and T2D (db/db), will be helpful in the discovery of new mitochondrial targets to promote energy expenditure in BAT and hopefully counteract obesity and its related complications. In detail, this project mainly focuses on:

1) Characterization of the sites of mtDNA (hydroxy)methylation
2) Characterizing the level and modifications of mtDNA-associated proteins and the effects on mtDNA transcription and replication
3) Determining consequences of mtDNA alterations on mitochondrial metabolism and nuclear transcription of metabolic genes normally expressed in active BAT

Carrying out this project will be useful for a better understanding of the role of excessive calorie intake on mtDNA trans-actions and its impact on mitochondrial metabolism and body energy homeostasis. Moreover, our current knowledge regarding the interactions of environmental calories with mitochondrial BAT metabolism will be invigorated, hoping that we can recruit and activate BAT to counteract obesity.