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EXPLORING MOLECULAR MECHANISMS OF SIRTUIN OF TYPE 1 (SIRT1) REGULATION IN A MOUSE MODEL MIMICKING CONSEQUENCES OF ANOREXIA NERVOSA

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Anorexia nervosa (AN) is known to impact bone quality. It was demonstrated in many studies using mouse models that Bone Marrow Adiposity (BMA) is increased in response to extended caloric restriction (CR) as described in anorectic patients. Sirtuin Type 1 (Sirt1), was shown to have pro-osteoblastic and anti-adipogenic effects. Therefore, we recently demonstrated that a 10-week energy deficit protocol (Separation Based Anorexia (SBA) model) inducing an 18% body weight loss, is associated with significant reduction of Sirt1 expression in Bone Marrow Stromal Cells (BMSCs).

Based on this finding we hypothesised that Sirt1 decrease in these cells is involved in bone and BMA alterations. To test this hypothesis we studied bone parameters and BMA at the proximal tibia, and BMSCs differentiation capacity, as well as Sirt1 expression after body weight loss (18%) during two periods of time (10 and 4 weeks).

In the current study 10-week SBA protocol resulted in alteration in bone parameters, BMSC differentiation and Sirt1 expression, similarly to previously published data (Louvet et al, 2020). To identify first changes that occur during CR, we decided to test the effect of short 18% weight loss protocol (4 weeks). Our results demonstrated that this protocol did not cause significant changes in bone parameters, BMA, BMSC differentiation or Sirt1 expression, despite the 18% body weight loss.

To study the potential molecular mechanisms involved in downregulation of Sirt1 after 10 weeks of SBA protocol, RNA sequencing was performed on BMSCs. Results were

complementing the initial qPCR findings of 10-week and 4-week cohorts regarding Sirt1 expression, as well as adipogenic/osteogenic markers. To identify pathways that are involved in Sirt1 regulation, we used results of 4-week RNA sequencing to subtract pathways that are not directly affecting Sirt1 expression. The rest of our search focused on 10-week protocol results. Through the R Studio program, analysis of the data was performed, we found 10 genes that potentially are interacting with Sirt1 within various downregulated pathways. Only Relb, CEBPb, Rara, Hif1a, Rb1, Esr1 were confirmed to be downregulated, therefore can be potentially involved in Sirt1 regulation. Additionally, transcription of AMPK, a known regulator of Sirt1, was found to be decreased in 18% SBA condition. The suppression of AMPK activity in BMSCs was shown to decrease AMPK mRNA level, as well as mRNA of Sirt1, suggesting the interaction between these two proteins.

In conclusion, our study showed that duration of energy deficit is involved in changes in bone parameters, BMSC differentiation capacity and Sirt1 expression. RNA sequencing helped to identify candidate genes that can interact with Sirt1. Additionally, AMPK suppression have been shown to decrease Sirt1 mRNA, suggesting the AMPK might also be involved in Sirt1 regulation. The prospects of this study is to perform functional test on target genes to establish the connection with Sirt1.