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## EXPLORING POTENTIAL REGULATORS OF SIRTUIN TYPE 1 (SIRT1) IN MOUSE BONE MARROW STROMAL CELLS (BMSC) FROM ENERGY DEFICIT MODELS

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It was demonstrated in many studies using mouse models that bone parameters are decreased in response to extended caloric restriction (CR). Sirt1 was shown to have pro-osteoblastic and anti-adipogenic effects. Recently demonstrated that a 10-week energy deficit protocol (Separation Based Anorexia (SBA)) of 18% body-weight loss, is associated with reduction of Sirt1 expression in BMSCs. Therefore, we hypothesised that in BMSCs, Sirt1 decrease is involved in bone alterations.

We studied bone parameters at the proximal tibia, BMSCs differentiation capacity and Sirt1 expression after SBA18% protocol, during 10- and 4-week. In the current study 10-week SBA protocol resulted in alteration in bone parameters, BMSC differentiation and Sirt1 expression. Additionally, we decided to test the effect of short (4-week) SBA18% protocol. Results demonstrated that 4-week protocol did not cause changes in studied parameters. To identify the potential molecular mechanisms involved in downregulation of Sirt1, RNA-sequencing and differential expression analysis was performed.

To identify pathways that are involved in Sirt1 regulation, we studied enriched pathways in 10-week cohort that are not present in 4-week, to eliminate pathways that are not affecting Sirt1. Our search focused on 10-week protocol results. We identified, using the Bioconductor R package cluster Profiler, genes that might be interacting with Sirt1 within various downregulated pathways. Additionally, transcription of AMPK, a known regulator of Sirt1, was found to be decreased in SBA18% condition. The suppression of AMPK activity in BMSCs was shown to decrease AMPK mRNA level, as well as mRNA of Sirt1, suggesting their interaction.

In conclusion, study showed that duration of SBA-protocol is involved in changes in bone parameters, BMSC differentiation capacity and Sirt1 expression. RNA-sequencing helped to identify candidate genes that could interact with Sirt1. AMPK suppression was shown to decrease Sirt1 mRNA. Currently, functional tests are performed on target genes to establish their connection with Sirt1.

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