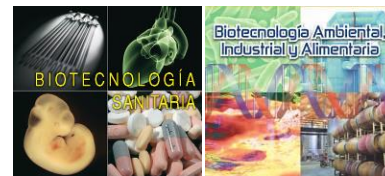


## Talk

## Restriction of cytosolic Acetyl-CoA to promote healthy aging



Eugenia Martin Vazquez (1), Anabel Rojas Gonzalez (1,2), Benoit Gauthier (1) and Alejandro Martin Montalvo (1)

(1) Cell Regeneration & Advanced Therapies Department, CABIMER, Americo Vespuccio, 24, 41092, Seville, Spain.

(2) Universidad Pablo de Olavide, ctra. Utrera, Km. 1, 41013, Seville, Spain.

**Keywords:** Acetyl-CoA; SB-204990; hydroxycitric acid; allicin; 1,2,3-benzenetricarboxylic acid

### ABSTRACT

**Motivation:** During the last century humans have reached the longest lifespan in History. However, the increase on lifespan is associated to the development of age-related diseases that limit the quality of life of aged individuals (1). Therefore, there is a current need to determine the molecular mechanisms underlining age-related pathologies and to develop novel effective therapies for these diseases. Acetyl-CoA (Ac-CoA) is a central metabolite in energy metabolism involved in protein acetylation, fatty acid synthesis and cholesterol synthesis (2,3), which may play a significant role modulating the intrinsic processes of aging. In this work, we studied the effects of 4 cytosolic Ac-CoA reducing agents; two inhibitors of the ATP citrate lyase; SB-204990 (SB) and hydroxycitric acid (HCA), an inhibitor of Ac-CoA synthase; allicin, and a inhibitor of the citrate isocitrate carrier; 1,2,3-benzenetricarboxylic acid (BTC).

**Methods:** Mice were fed a Standard Diet (STD) or a High Fat Diet (HFD) supplemented with SB for 15 weeks. After in vivo studies, we performed WB on metabolic tissues. In liver tissue we performed a proteomic analysis by iTRAQ (Isobaric tags for relative and absolute quantification). In parallel, we have initiated a longevity assay using HCA. Necropsies have been performed to determine the cause of death. Finally, we are currently investigating the effects of BTC and allicin in murine physiology using three experimental approaches; a healthy STD, a prophylactic treatment using an obesogenic/diabetogenic HFD and a therapeutic treatment used in obese mice.

**Results:** Preliminary in vivo results have shown improvements in metabolic health on mice treated with SB. Ex vivo analyses have indicated that SB modulates lipid metabolism. Proteomic analyses revealed a decrease in the expression of proinflammatory proteins in SB-treated and HFD-fed mice. HCA supplementation in healthy STD-fed mice has resulted in delayed early mortality in mice. Additionally, HCA treatment revealed potential benefits in muscle strength in wirehang test. Our research using BTC and allicin will generate results in the nearly future.

**Conclusions:** Results of SB-treated and HFD-fed mice show a robust modulation in lipid metabolism and in inflammatory pathways, suggesting that the intervention could rescue the phenotype associated to a metabolic deregulation. The improvements observed in HCA-treated mice suggest that HCA could have geroprotective effects in early mortality.

### REFERENCES

1. World Health Organization. Regional office for Europe. 10 facts on healthy ageing in Europe.
2. Pietrocola, F., Galluzzi, L., Bravo-San, J.M., Madeo, F. and Kroemer, G. (2015) Acetyl Coenzyme A: A Central Metabolite and Second Messenger. *Cell Metabolism* 21.
3. Eisenberg, T., Schroeder, S., Andryushkova, A., Pendl, T., Kuttner, V., Bhukel, A., Marin, G., Pietrocola, F., Harger, A., Zimmermann, A., Moustafa, T., Sprenger, A., Jany, E., Buttner, S., Carmona-Gutierrez, D., Ruckenstein, C., Ring, J., Reichelt, W., Schimmel, K., Leeb, T., Moser, C., Schatz, S., Kamolz, L-R., Magnes, C., Sinner, F., Sedej, S., Frohlich, K-U., Juhasz, G., Pieber, T. R., Dengjel, J., Sigrist, S. J., Kroemer, G. and Madeo, F. (2014) Nucleocytosolic Depletion of the Energy Metabolite Acetyl-Coenzyme A Stimulates Autophagy and Prolongs Lifespan. *Cell Metabolism* 19, 431–444.