Metabolic flexibility: breaking down food effectively to prolong life

Informe

Información del proyecto

MetaFlex

Identificador del acuerdo de subvención: 638290

Sitio web del proyecto

DOI
10.3030/638290

Proyecto cerrado

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Periodic Reporting for period 4 - MetaFlex (Metabolic flexibility: breaking down food effectively to prolong life)

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Resumen del contexto y de los objetivos generales del proyecto

Worldwide, populations are aging progressively, which goes along with a burden of age-associated diseases that have a strong personal and economic impact on those affected, but also on society as a

whole. Although reduced caloric intake and increased exercise improve health, Western societies are dominated by fat-enriched diets and lack of exercise. Therefore, caloric restriction and exercise mimetics have been developed that reproduce the benefits under population-wide realistic caloric intake or exercise efforts. The identification of a novel anti-aging pathway will not only give more insight in the basic biology of aging, but also open new avenues for targeting age-related diseases.

Aging has long been considered a passive process. More recently studies have defined an important, active role for metabolic pathways in aging and age-related diseases. We have previously demonstrated a marked dysregulation of fat metabolism in aged mice that contributes to their overweight and glucose intolerance. The MetaFlex model links healthy aging to efficient processing of nutrients, a state termed metabolic flexibility: reducing protein or carbohydrate metabolism will strongly stimulate fat breakdown. We suggest that improved metabolic flexibility will prevent the accumulation of lipids and protect against its detrimental effects.

The main goal of this project was to further clarify the link between metabolism and aging.

Trabajo realizado desde el comienzo del proyecto hasta el final del período abarcado por el informe y los principales resultados hasta la fecha

Over the course of the project, our team identified biomarkers of aging, new mechanisms of aging, and potential dietary and pharmacological interventions to promote healthy aging at least in model organisms.

Biomarkers:
Biomarkers are important to track the development of aging or age-related disease in individuals. It might help to identify individuals who would benefit from interventions. We used lab worms (C. elegans) and tissues from mice in which we performed analysis of metabolic compounds, including fats and amino acids. We found signatures of aging in these worms/tissues that can discriminate between young and aged individuals. We are currently testing if these signatures also apply to older humans. Moreover, it enabled us to develop new treatments and identify new mechanisms.

Mechanisms:
We previously found a gene that, when shut down, extends lifespan in worms by 60%. We only partly understood how this worked and investigated it further. We found that there is an important role for protein synthesis is this process, but also that it's influenced by the shape and form of mitochondria, the powerhouse of our cells. We also established new mechanisms that explain the susceptibility to fat diets in worms. We found a specific gene that renders worms protected against the harmful effects of such a fat diet, but follow-up work will need to confirm if the same applies to humans.

Interventions:
From our biomarker screens in worms we found that the amino acid glycine accumulated with age. We tested if this was the cause for or consequence of aging by supplementing glycine to worm. Such

supplementation led to a marked extension of lifespan, suggesting that glycine has a protective effect. We also did a computer-based test to identify pharmacological compounds that could prolong lifespan. Through this approach we found a specific muscle relaxant that extends the lifespan in worms. Although this is unlikely to work the same in humans, it provides new leads for research into alternative approaches that might work in humans too.

Avances que van más allá del estado de la técnica e impacto potencial esperado (incluida la repercusión socioeconómica y las implicaciones sociales más amplias del proyecto hasta la fecha)

Scientific impact:
As our research is at the forefront of the metabolic aging field, we are continuously improving the state-of-the-art technologies that are required to answer our research questions. For instance, we developed several platforms for the measurement of metabolites and metabolic fluxes in C. elegans, cells, mouse and human tissues. These methods are getting increasingly popular and we receive many requests for collaboration.

Societal impact:
-Considering that we primarily work with the worm C. elegans, there is still a long way to application in humans. Nevertheless, through collaboration with clinical research groups we are currently translating our findings as many of the concepts we work with can be applied to other fields of research as well. For instance, we are collaborating with leaders in the field of immunometabolism who apply our concepts of metabolic flexibility to their cell system. The same is true for projects on adipose tissue and cardiac metabolism.
-We are seeking outreach opportunities to enlighten the general public but also policy makers about blue sky research. For instance, my research was featured in the ERC-supported Science Squared campaign “The Taste Tests”, http://www.sciencesquared.eu/taste-tests and I participated as a speaker at the meeting “Research Strategies: Europe 2030 and the next Framework Programme” (http://sciencebusiness.net/events/2016/research-strategies-europe-2030-and-the-next-framework-programme/). Furthermore, we started a Facebook page where we share our progress and events we participate in. We also made a short movie that explains our work in simple terms: https://youtu.be/Mx4mhLgAT20.

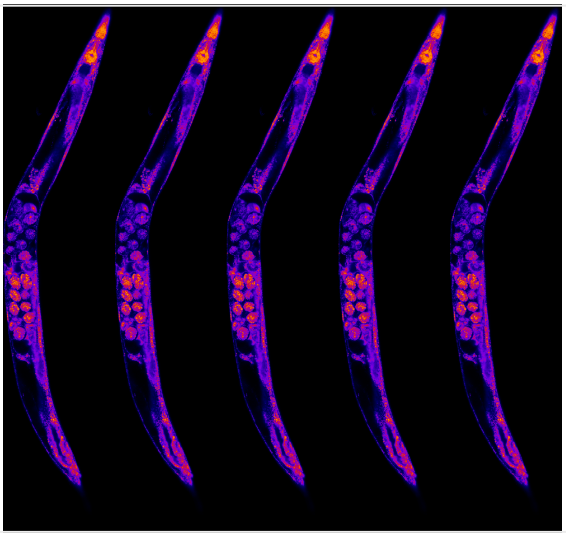

Image of a worm, the main model organism of MetaFlex project

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