Caloric Restriction and Aging

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Introduction

Aging is characterized by the **functional decay of the body**, being the primary risk factor for a multitude of pathologies. This process is characterized by common cellular and molecular traits, the **Hallmarks of Aging**, that are highly interconnected reflecting the complexity of this process. **Caloric restriction** (CR) is defined as the **reduction of the nutrient intake without malnutrition**, normally between a 20-40% of the caloric intake. Studies as far as 1935 provided evidences that caloric restriction reduced the growth and delayed the aging. Caloric restriction arises as **intervention to delay aging** and postponing or attenuating the related pathologies at once.

Objectives and Methodology

The aim of this bibliographic revision is to understand the different mechanism involved in aging and how the molecular mechanism triggered by caloric restriction may influence this processes and more specifically its effects on the brain.

In order to do so, an extensive bibliographic search has been done given specially focusing on reviews and the more recent articles on the different key parts of this project.

HORMESIS

The restriction of nutrients acts a **moderate stressor,** eliciting several adaptative responses.

The direct consequences of the caloric restriction are changes in the energy balance and in the NAD^+/NADH ratio that will effect the activity of three **key metabolic sensors**; mTORC, AMPK and the protein family of the sirtuins, that would mediate the majority of the molecular effects.

These enzymes do regulate one another and modulate the effects of the different downstream elements at different points, establishing a complex network.

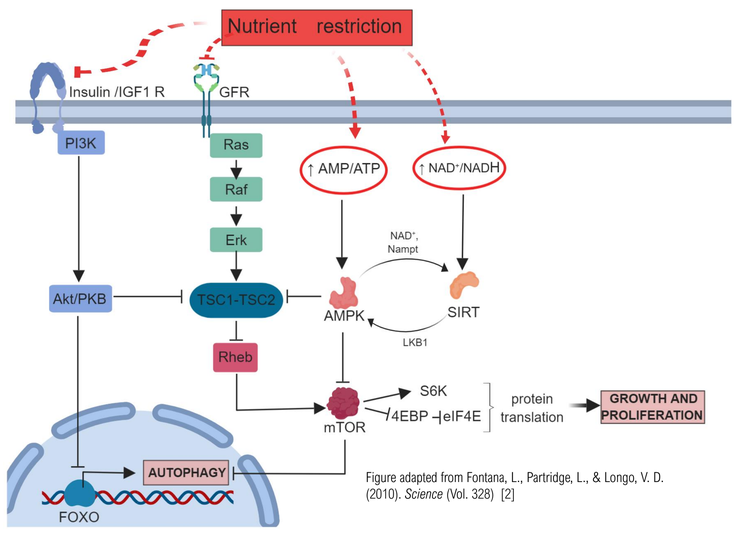

Figure adapted from Fontana, L., Partridge, L., & Longo, V. D. (2010). *Science* (Vol. 328) [2]

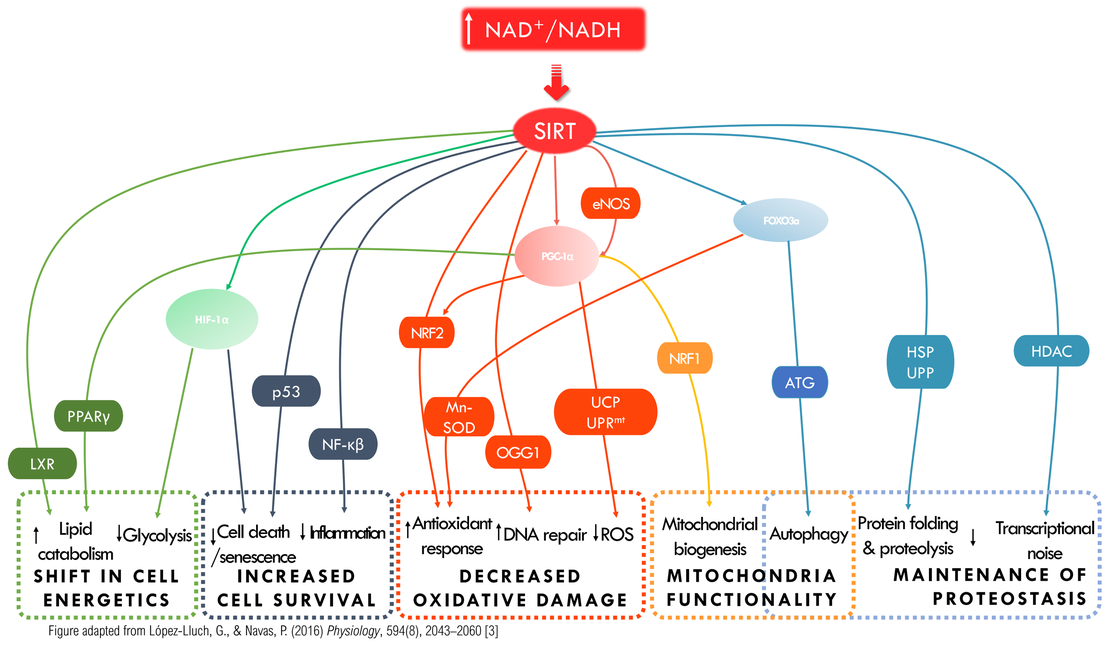

Figure adapted from López-Lluch, G., & Navas, P. (2016) *Physiology*, 594(8), 2043–2060 [3]

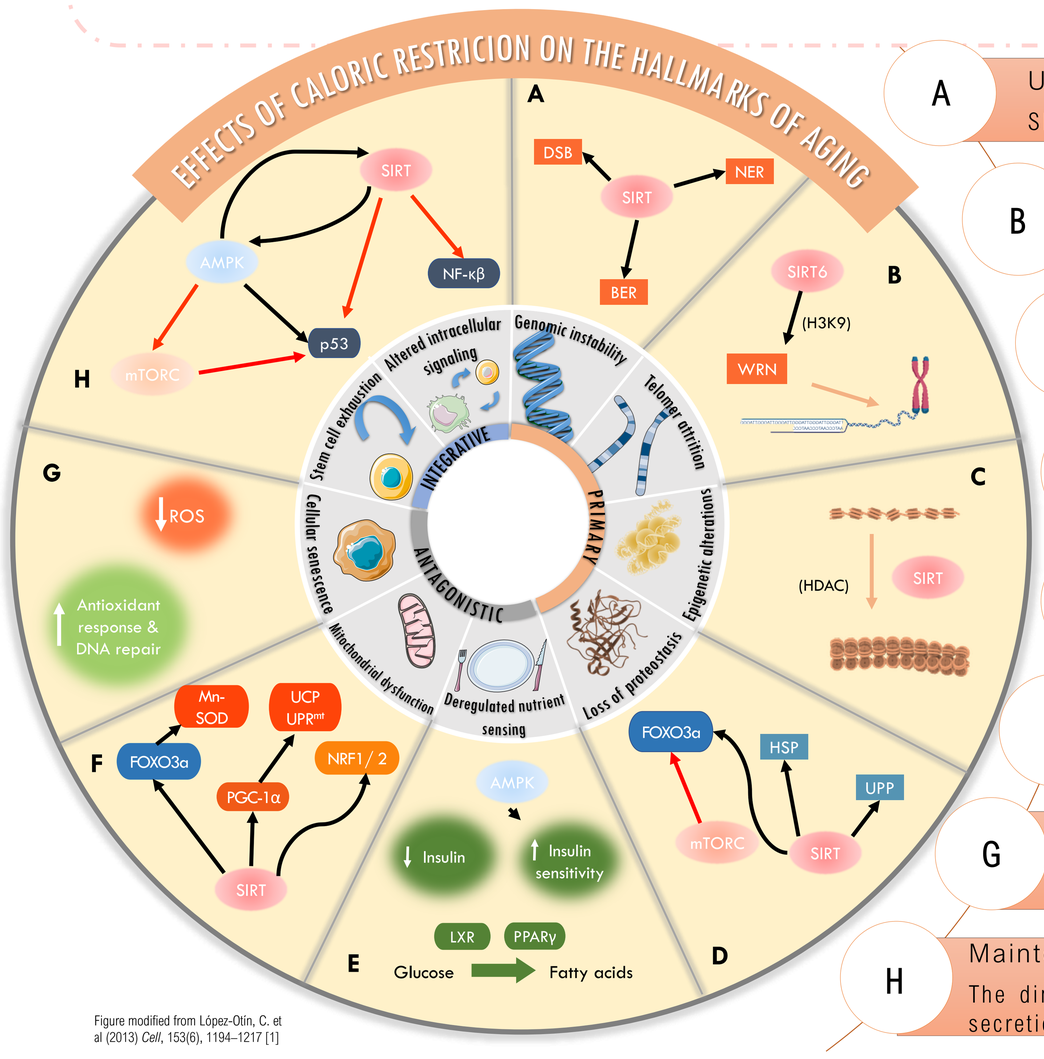

Figure modified from López-Otín, C. et al (2013) *Cell*, 153(6), 1194–1217 [1]

A — Upregulation DNA repair

SIRT upregulates the different DNA repair mechanism by regulating several enzymes involved in the DDR

B — Stabilization of the telomere

SIRT6 deacetylases H3K9 promoting the stabilization of WRN in the telomere

C — Diminished transcriptional noise

SIRT through deacetylation in H1K26, H4K16, H3K9 and H3K56 promotes the formation of heterochromatin

D — Enhanced clearance of dysfunctional proteins

Increased activity of FOXO3a promotes the expression of genes involved in autophagy and the proteosomal pathway. Additionally, activation of HSP-1 promotes the expression of chaperones.

E — Enhanced insulin sensitivity

Metabolic switch from using glucosa towards fatty acids. The decrease in glucose and insulin, in addition to the activation of AMPK translates as an increase in the insulin sensitivity.

F — Heighten mitochondrial turnover and increased efficiency

Stimulation of mitophagy and mitochondrial biogenesis. Expression of genes involved in the antioxidant response and the OXPHOS cycle allow a similar ATP production but a diminished generation of ROS

G — Avoidance of senescence

Decrease in the potential stimulate that may trigger the senescence by the diminished ROS damage and the enhanced protective mechanism

H — Maintenance of the stem cell pool and tissue homeostasis

The diminished damage and the inhibition of p53 promotes the survival of the cell. Additionally by downregulation the NF-κβ the secretion of pro-inflammatory cytokines is diminished, avoiding the altered communication.

COMMON
- Mitochondrial dysfunction
- Increased oxidative damage
- Loss of proteostasis
- Impaired DNA repair
- Altered energy metabolism

BRAIN-SPECIFIC
- Dysregulated Ca homeostasis
- Aberrant neuronal network activity
- Impaired neurogenesis

CELLULAR AND MOLECULAR ALTERATIONS OF AGING BRAIN

The decline of the brain exhibits an **impairment in the individual's cognition**. All the different alterations mentioned above lead to the loss of the structural integrity of the neural circuits and the atrophy of the brain.

CR

<u>Nutrient restriction</u>, upregulation of stress response promoting cell survival: Antioxidant defences, DNA repairment, autophagy, anti-inflammatory, Ca^{2+} homeostasis and mitochondrial functionality.

<u>Recovery</u>, activation of biosynthetic activities:
- Synaptic plasticity
- Neurogenesis

MAINTENANCE OF THE PROPER COGNITIVE FUNCTIONS

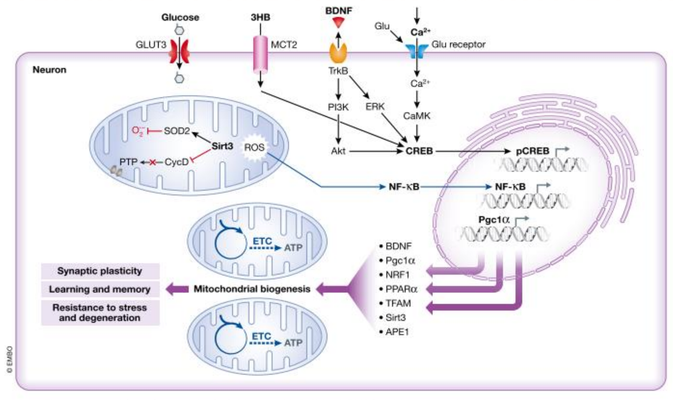

Figure extracted from Camandola, S. & Mattson, M. P. (2017) *EMBO J.* 36, 1474–1492 [4]

There is a huge interest in the retardation of aging and the treatment of related pathologies, such as cancer or diabetes. The so called caloric restriction mimetics are **pharmacological agents** that duplicate some aspects of the caloric restriction.

- Metformin, an AMPK activator, commonly used for the treatment of diabetes.
- Rapamycin, an inhibitor of mTORC. Mainly used as an immunosupressor.
- Sirtuins activators, such as **resveratrol.**

All these drugs are or have been used in a multitude of clinical trials, which shows not only their relevance but also the importance in the search for transversal interventions.

Conclusions

Caloric restriction triggers evolutionary conserved mechanism that allow the survival of the organism until more permissive circumstances arise and allow the reproduction. The activation of few nutrient sensing molecules **activated by the changes in the energy balance and redox status** is enough to trigger the adaptation of the whole body that translate into the **extension in the lifespan**. The extend of the caloric restriction can be summarized in two main standpoints, the **decrease of the generation of damaging agents and the enhancement of the repair mechanism.** Caloric restriction by the delay of the different cellular and molecular alterations associated with brain aging can **retard the neurodegeneration and the impairment in the cognition,** which demonstrate that caloric restriction not only has a pro- longevity effect but also postpones the onset of aging related pathologies.

References

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2. Fontana, L., Partridge, L. & Longo, V. D. Extending Healthy Life Span: From Yeast to Humans. *Science* 328, (2010)
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5. Mattson, M. P., Moehl, K., Ghena, N., Schmaedick, M. & Cheng, A. Intermittent metabolic switching, neuroplasticity and brain health. *Nat. Rev. Neurosci*. 19, 63–80 (2018)