Insights into human extreme longevity from studies on Dermal Fibroblasts

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Human aging is a complex phenomenon yet not totally understood in its molecular mechanisms. However, it is generally believed that aging of the organism is largely determined at cellular level. A helpful model for disentangling the mechanisms of aging is represented by Dermal Fibroblasts (DFs). Our group was among the first to describe the characteristics of DFs obtained from subjects of extreme old age such as centenarians, who can be considered the best example of successful aging. Taking advantage of this model, we have performed over the years a number of studies allowing us to determine that DFs from centenarians most often share features with those from young people rather than 70-80 years-old persons. Just as an example, we were able to assess that proliferative capability and telomere length are quite well preserved in DFs from centenarians and that they express high levels of p66shc protein.
More recently, we assessed the bioenergetics of these cells and discovered that, besides some defects in the respiratory chain and production of Reactive Oxygen Species, DFs from centenarians have a preserved capability to generate ATP thanks to a large network of elongated mitochondria resulting from a successful mitochondria remodelling that can compensate for functional defects through an increase in mitochondrial mass. We also demonstrated that DFs from centenarians are characterised by loss of heterochromatin linked to prelamin A accumulation, with a concomitant recruitment of the inactive form of 53BP1, associated with rapid response to oxidative stress. Interestingly, these effects can be reproduced by rapamycin treatment of cells from younger individuals (70 yo).
We propose that, as a whole, DFs from centenarians are characterised by a series of adaptive mechanisms (e.g. increase of mitochondrial mass, recruitment of DNA repair proteins) to quickly and effectively respond to stress stimuli, and that a preserved stress response is likely one of the most important mechanisms to safeguard healthy ageing.