Caloric Restriction Promotes Fur Remodeling as a Thermoregulatory Mechanism

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Caloric restriction (CR), the limitation of dietary calories without lack of essential nutrients, extends the lifespan of a variety of species, including yeast, worms, flies and mice. Among the many effects of this diet, recent results show that it affects stem cells, responsible in mammals for the maintenance and replacement of tissues throughout life. Furthermore, many aspects of mammalian aging can be related to a decline in the replicative function of stem cells. In order to investigate the impact of CR on stem cells we submitted swiss female mice to 6 months *ad libitum* (AL) or 60% of the total calories (40% CR) and observed the impact on the skin and associated stem cells. The first observation was that CR backskin fur coat was more even and long due to an increase in guard hair follicle density and length ($p \leq 0.001$). The thickness of the epidermis was also increased in the CR group, in detriment of the hypodermis ($p \leq 0.05$). Hair clipping experiments also demonstrated that both synchronized and unsynchronized hair follicles show increased growth rates ($p \leq 0.05$), most probably due to early stem cell recruitment. In accordance, the pool of β1-integrin^{+} interfollicular (IFSC) and β1-integrin^{HIGH}/CD34^{+} hair follicle-associated epidermal stem cells (HFSC) was significantly increased ($p \leq 0.05$ and $p \leq 0.001$, respectively). The bioenergetic profile of both epidermis and dermis was evaluated. CR epidermis presented increased glycolysis, while the dermis displayed a significant increase in spare and maximal mitochondrial respiration. This metabolic shift culminates in phenotypic alterations that are significant for thermoregulation. Remarkably, when the fur was removed, CR animals displayed defective thermoregulation associated with rupture of locomotion patterns and lean weight loss ($p \leq 0.001$). In brief, these findings unveil not only a striking effect of CR upon stem cells, but also an important evolution-selected adaptative mechanism to cope with reduced insulation derived from a thinner hypodermis.

Keywords: skin, calorie restriction, thermoregulation, hair follicle stem cell, bioenergetics

Supported by: FAPESP, CNPq, Guggenhein Foundation.