

CONNECTION BETWEEN LONGEVITY AND THE STRESS RESPONSE THROUGH PGC-1a

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Although it is well established that caloric restriction (CR) extends lifespan, little is known of the underlying mechanism or the identity of the key factors involved. Evidence from transgenic models indicates that perhaps longevity and the stress response are mechanistically connected raising the possibility that there are shared pathways and common factors. Transcriptional profiling of tissues from control and CR mice reveals evidence for a CR-induced shift in energy metabolism and a coordinated increase in the expression of nuclear genes encoding mitochondrial proteins. We have identified the transcriptional co-activator PGC-1a as one of the factors that may be involved in the mechanism of lifespan extension by CR. PGC-1a is a key regulator of mitochondrial energy metabolism but also plays a more general role in energy homeostasis through its interactions with the peroxisome proliferator activated receptors. PGC-1a protein levels are elevated in multiple tissues of CR mice and the expression of gene targets of PGC-1a are up regulated. PGC-1a is also induced in skeletal muscle of mice that have been subjected to oxidative stress. These data indicate that PGC-1a is one of the factors common to CR and the stress response. The activation of regulatory kinases is a central feature of the stress response and we have detected stress kinase activation in tissues from CR animals, supporting the concept that there is a mechanistic overlap between these two adaptive processes.