

## **METABOLIC RE-PROGRAMMING IN RESPONSE TO CALORIC RESTRICTION**

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CR extends maximum lifespan in many species and in mice there is a linear inverse relationship between calorie intake and extension of lifespan. One hypothesis to explain aging retardation by caloric restriction (CR) is that it triggers an active response involving a reprogramming of energy metabolism. Using Affymetrix microarrays, we have examined transcriptional changes with age and CR in multiple tissues. In mouse heart, diverse transcriptional alterations occur with aging that are consistent with a metabolic shift from mitochondrial fatty acid oxidation to carbohydrate metabolism. These alterations, which are also observed in pathological heart conditions, are completely or partially prevented by CR. We have mined the microarray data further and discovered potential upstream regulators of CR's actions. Notably, the expression of the metabolic regulator PGC-1 $\alpha$  is upregulated by CR in heart as it is in epididymal white adipose tissue (WAT) and liver. We have also studied the effects of CR on WAT in mice and observed 70% reductions in depot weight and adipocyte size and again observed overt metabolic reprogramming. CR induced a concerted upregulation in the expression of nuclear-encoded genes involved in mitochondrial energy metabolism. This was functionally confirmed by measuring histochemically the activity of Complex IV. Lastly, we have submitted a manuscript focused on the genes downregulated by CR in WAT. Of the 198 genes downregulated by CR, 55 genes (28%) were classified as involved in inflammation. Only one gene so classified (adipsin) was observed to be upregulated by CR. We suggest that major changes induced by CR include metabolic reprogramming in multiple tissues and a beneficial lowering of WAT-derived systemic inflammation. *Supported by grants from the NIA.*