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Rapid identification of candidate CR mimetics using microarrays

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Quantitative changes in the activity of genes can control the rate of aging and the development of age-related diseases in invertebrates and mammals. Caloric restriction (CR) is the most robust environmental method known for decelerating aging and the development of age-related diseases. CR is widely viewed as acting slowly and incrementally to prevent the accumulation of deleterious age-related physiological changes. CR is also widely thought to be less effective in older animals. Using survival and high-density microarray studies we demonstrate that CR acts rapidly and reversibly to establish a pattern of gene expression temporally associated with enhanced life span and reduced tumor incidence in mice. CR was fully effective at extending life span and reducing tumor incidence when begun in old animals. The results indicate that therapies mimicking the gene expression effects of CR may be rapidly effective, even in old animals. To investigate this possibility, we screened three glucoregulatory pharmaceuticals and a soy isoflavone extract (a putative chemopreventative) for their ability to mimic the effects of long-term CR on gene expression using hepatic RNA, since most of these mice die of liver tumors. The glucoregulatory pharmaceuticals and the combination of two of these pharmaceuticals produced a significant number of changes in hepatic gene expression identical to those produced by long-term and/or short-term CR. The most extensive overlap with CR was obtained from metformin. The gene expression changes common to metformin and CR were associated with xenobiotic metabolism, cellular stress, energy metabolism, biosynthesis, signal transduction, and the cytoskeleton. The changes are consistent with enhanced apoptosis and protein turnover, and reduced tumor incidence and cellular stress. These results suggest that metformin is potential CR-mimetic. Others have shown that phenformin, a glucoregulatory pharmaceutical structurally and functionally similar to metformin, extends the lifespan of mice by 23%, and reduces cancer as a cause of death from 80% to 20%[1]. Others recently have presented preliminary evidence that metformin extends the lifespan of rats[2]. Therefore, agents that reproduce the long-term CR signature in microarray assays are candidate CR mimetics.

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1 Dilman V.M. & Anisimov V. N. Effect of treatment with phenformin, diphenylhydantoin or L-dopa on life span and tumour incidence in C3H/Sn mice. (1980) Gerontology 26:241-246.

[2] Roth G. Platform presentation at the National Institute on Aging Caloric Restriction Symposium, Mayan Ranch, Bandera, Texas, November 2002.