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editorial focus

# *In for the long run*: Focus on "Lifelong voluntary exercise in the mouse prevents age-related alterations in gene expression in the heart"

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WHILE IT IS KNOWN that exercise has an effect upon aging and lifespan in rodents, what is not yet well understood is how exercise ameliorates the deleterious effects of aging at the cellular level. Microarray analysis makes it possible for researchers to assess changes in mRNA transcript levels in particular tissues which may translate into significant changes in protein levels. Thus a better understanding of the functional genetics of exercise can provide insight into the physiological genomics of the aging process.

In this release of *Physiological Genomics* (Ref. 2; see page 129 in this release), Bronikowski et al. (2) employ expression profiling of mouse hearts to examine age- and exercise-related changes in gene expression. Their goal was to assess the changes in gene expression that occur in the hearts of both sedentary and active mice and to determine what effect exercise had upon genes demonstrated to be differentially regulated in the sedentary animals. They used male mice drawn from an ongoing breeding program, now past its 16th generation, that selects individuals with a predilection for voluntary exercise. In the experimental group, the mice were given free access to a running wheel (the "active" group); control animals (the "sedentary" group) were housed in cages without one. Subjects' hearts were harvested and assayed at midlife (20 mo) and old age (33 mo) by hybridization to an Affymetrix mouse cDNA array. The only previous study of age-related changes of gene expression profiles in the heart involved left ventricular cardiomyocytes extracted from 4-mo-old and 20-mo-old C57BL/6 mice (1).

In keeping with previous findings, the authors demonstrated that exercise increased the median, although not the maximum, lifespan of the active mice (by 17%). The expression of 137 genes changed by at least 50% between old and younger mice in the sedentary group. Changes in 70 of these same genes were significantly attenuated in the exercise group. In addition, fewer genes were significantly affected by age in the active vs. sedentary mice. In the sedentary population, the major classes of differentially expressed genes were associated with inflammation and stress response, leading the authors to conclude that the aging heart experiences oxidative stress leading to a pro-inflammatory state. Interestingly, these changes were attenuated even though very old active mice exercised much less than they had in their youth.

This study is encouraging for those of us who try to exercise on a regular basis to ward off the functional decline associated with aging. Bronikowski et al. studied only the heart, but previous expression profiling studies suggested that aging also increases oxidative stress and inflammation in skeletal muscle and brain (3, 4). Whether the exercise produced systemic effects that would inhibit this aspect of aging in all organs, or whether it only produced local effects caused by the increased workload of the heart and exercising muscles, is an important question that will require additional research.

The conclusions based on any exploratory analysis need to be confirmed prospectively before they can be fully accepted. One of the pitfalls in interpreting studies of exercise, caloric restriction, or other anti-aging interventions is the problem of regression to the mean. Whenever thousands of variables (mRNA levels in this case) collected from 3–4 animals are compared with data from 3–4 other animals, there are many statistically significant differences by chance alone (due to real heterogeneity among animals, not necessarily measurement error). When two other independent groups are compared, the differences between the first two groups that were caused by sampling error are absent or attenuated. If the first set of animals is used to define ordinary aging, and the second set undergoes an anti-aging intervention, then the anti-aging treatment may get undue credit. When specific genes are

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hypothesized to behave this way a priori, there is very strong evidence that the anti-aging intervention is responsible. Post hoc conclusions from exploratory studies are more tentative. In this particular study, however, there were some reassuring data to suggest that regression to the mean cannot explain the apparent effect of exercise on gene transcription. First, statistical methods suggested that no more than 10% of the age-related differences should be attributable to sampling error, whereas many more of them were reversed by exercise. Second, in exercising animals only half as many genes were affected by aging, an effect that cannot be explained by regression to the mean.

The "middle-aged" mice would be comparable to 75-yr-old humans in terms of the age at which half of the population has died. The old animals must be considered extremely old for this line of mice, since only 5% of them survive to 31 mo of age. Thus Bronikowski et al. examined a very select group of mice at the oldest age. Moreover, all mice in the study were selected for their high volume of voluntary treadmill running. These issues raise several questions that warrant further investigation. Do the age-related changes in gene expression observed in this study occur only near the end of life? Would access to treadmills have a similar effect in ordinary mice? Would forced exercise have the same effect as voluntary exercise, or would it have the opposite effect? How much exercise is needed to retard aging at the level of gene expression?

Microarray data provide only a starting point for expanding our knowledge of the molecular basis of factors that influence the rate of aging. Additional studies are needed to determine which cells within the tissue are affected, whether effects are focal or diffuse, and which of the changes in gene expression are physiologically significant. Questions about the physiology of aging have sent many investigators to the microarray laboratory, and now tables full of microarray data should be sending investigators back to the physiology laboratory with new ideas.

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