Biomarkers of Aging

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A MAJOR question for research on aging over the last two decades is the difference between “aging” and disease. How, in fact can one separate the two? Differing views on this question underlie many of the differences in scientific and policy opinion about aging and its personal and societal consequences. Biomarkers of aging, if they are truly markers of basic biological processes, rather than disease, would greatly inform such discussions. By the same token, if one believes that aging and disease are different aspects of the same processes, then a biomarker of aging will always be a marker of one or another disease as well. Ultimately, this is an empirical question, not a philosophical one, though it may also be unanswerable with complete certainty. Does it matter? If your interest is in understanding aging processes, then the answer is yes. If, on the other hand, you want to predict disability for purposes of public policy, the answer may well be no. If you want to sell biomarker of aging tests to physicians and insurance companies, then you probably only want the appearance of validity. All three of these views of the need for and utility of biomarkers are currently readily available in the scientific and lay literature. The views of all of us who participate in research in this area are colored by our exposure to varying aspects of these views and where we encounter them. My own interest in biomarker research began in about 1981 when the biomarker concept was reasonably focused and most investigators knew what was meant by the term. It was also true back then that the concept of biomarkers was quite controversial. In the two decades since then, the biomarker concept has been accepted by large parts of the scientific and policy-making communities, if not by all gerontologists. In fact, “biomarker of aging” has become a buzzword, useful to scientists arguing for more congressional funding and to various factions of the health care complex with products to sell. How did we get to this point?

In the early 1980s people in developed nations around the world were becoming increasingly aware of the inevitability of aging and of the impending large increases in the aging proportions of populations. As aging and its problems became more and more a topic of individual and public policy concern, interest in interventions to delay or slow down aging also grew. An important question in all research on this topic is how to separate science from pseudoscience. The opportunities for fraud and quackery are enormous in the aging intervention arena, and no opportunity is currently left unexploited.

The growing interest in interventions coincided with a growing research interest in understanding basic aging processes and in finding ways to measure “rate of aging.” At a personal level, each of us can make some reasonable judgements about the rate at which some individuals around us are aging. We know individuals who appear to be aging slowly and others who appear to be aging quickly, and we are very often correct in those judgements. This ability, if we can call it that, leads us to believe that “rate-of-aging” anagrams exist. This makes all of us, but especially the general public, vulnerable to sophisticated biomarkers of aging pseudoscience.

The concept of biomarkers rests on the assumption that the passage of time is only indirectly related to age. If, in a biological sense, the life span of a mouse and that of a man are equivalent, then the passage of time is a very poor measure of age. Interventions into aging processes could produce equally significant differences in the rates of aging of individual members of a single species. Biomarkers would be measures, which could be obtained in a small portion of the life span, that accurately reflect rate of aging and therefore predict longevity.

In all likelihood, aging is the cumulative product of multiple basic mechanisms. Because interventions may affect one or more of these mechanisms, it is crucial that biological markers of aging measure multiple functions. Thus, is it usually assumed that a “panel” of biomarkers will be required in order to assess the rate of aging of any individual animal or group of animals being treated by an “anti-aging” intervention?

What are the desirable features of useful biomarkers?

1. Biomarkers should be able to be assessed in a nonlethal manner in animal models and should not cause trauma in humans.
2. Biomarkers should be highly reproducible and reflect physiologic age.
3. The function examined should display significant alterations during relatively short time periods.
4. The clinical functions being measured should be important to the effective maintenance of health and function.

Although progress is being made in developing biomarkers of aging, it is too early to constitute a definitive panel of biomarkers for either animal models or humans. The “biomarker” panels touted by the “longevity medicine” industry are not validated in any population. Progress is being made, however.

The reports in this issue are a part of the results of a National Institute on Aging (NIA) initiative begun in 1988 to develop valid biomarkers of aging. At that time, the NIA, together with the National Center for Toxicological Research, created a colony of inbred and hybrid rats and mice specifically for biomarker research. Because caloric restriction (CR) was then the only known intervention to produce life span extension reliably, the biomarker research colony included ad libitum-fed and calorically restricted mice and rats. Animals from this colony were provided to investigators for biomarker research.
The reports in this issue are among the first to summarize the results of this broad initiative. Although the initiative was designed to study potential biomarkers of aging, understanding the mechanisms of the CR effect proved irresistible to most investigators. Some of the reports in this issue focus on the biomarker issue directly, whereas others reflect the interest in mechanism.

A very significant objective of the NIA initiative was to fully characterize the commonly used NIA-provided rat and mouse models for aging research. This characterization is important to all investigators who use such animal models, but is rarely supported by the reviewers of the grant applications that make use of the animals. The reports by the Bronson/Lipman group (pp. B466–B491) in this issue are a major contribution to the utility of rodent subjects in aging research. These reports speak most directly to the question of the difference between aging and disease. Although the reader may not agree with all of the conclusions of Drs. Bronson and Lipman, their point of view is well supported and certainly deserves serious consideration by all investigators in this arena. At the very least, they are telling us that much of what is currently considered “normal aging” is really the end product of a disease process. The consequences of this assumption for approaching the alleviation of the frailties of our aging population are enormous.

The report by Turturro and colleagues in this issue (pp. B492–B501) completes the much-needed characterization of our animal models. The food consumption, body weight, and survival data for four mouse genotypes and three rat genotypes most commonly used for aging research should be of very significant utility to every investigator who uses these animals. There are data (Bronson & Lipman and Turturro et al.) that the investigator should explore carefully before choosing a model for research, not after a commitment is made to any one or more genotypes.

The “review” by Drs. Wolf and Pendergrass (pp. B502–B517) places their research for cell senescence biomarkers in the broader context of cell senescence research. A great deal of current controversy in this area revolves around the question of whether in vitro cell senescence has any relationship to senescent events in vivo. This report reviews a broad range of relevant literature and relates it to the experiments conducted by these investigators with the NIA/NCTR rodent colonies and other models as well. Relationships among the effects in vitro and in vivo in ad libitum and CR animals are explored and related to possible mechanisms of aging.

Dr. Friedman and his colleagues report on studies of protein kinases in brain cells in the biomarker rats (December issue). MAPKs are involved in regulating important cell functions including apoptosis and neurotransmitter regulation. Although the Friedman group has not yet succeeded in establishing reliable kinase biomarkers of aging, they have demonstrated clearly that aging impairs kinase function in the brain. CR attenuates the effects of aging. The importance of understanding the decline in kinase activity for normal and pathologic events that accompany aging in the brain is evidenced by the devastating consequences of impaired brain function in elderly persons.

Perhaps the ultimate expression of brain function is behavior. Drs. Markowska and Becker (December issue) report on studies to characterize behavioral change with age, observe the effects of CR upon those changes, and identify potential behavioral biomarkers of aging. The behavioral measures covered a very broad range of behaviors including learning, memory, and sensorimotor skills. Dr. Markowska developed a multivariate statistical strategy to manage the extensive set of measurement values and to approach the task of finding multimeasure biomarkers. Multimeasure or component scores are likely to be more useful than single measures, because they are likely to be representative of higher level physiological functions and therefore more generalizable.

One of the liveliest controversies in aging is the importance of hormone decline with advancing age. Many hormones do decline, and there is an enormous interest in hormone replacement therapies. This interest is clearly evident in the response of the nutritional supplement industry as well as in the rapid proliferation of “rejuvenation clinics” that have hormone replacement as the major tool in their armamentarium. Growth hormone is one of the most intensely studied hormones in this arena. Dr. Sonntag and his group (December issue) report on the effects of growth hormone decline, the effects of CR on the alleviation of those declines, and the possible mechanisms on the CR effect. One of the problems of hormone replacement therapies is the increased risk of some types of cancers. This report examines the interaction of growth hormone and IGF-1 and suggests a possible mechanism for this increased risk and a mechanism for the reduction in tumor frequency with CR as well.

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