Guest Editorial

Are Glycans the Holy Grail for Biomarkers of Aging? (Comment on: Glycans Are a Novel Biomarker of Chronological and Biological Age by Kristic et al.)

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Posttranslational modifications of circulating proteins such as immunoglobulins may prove to be important biomarkers of aging.

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EVALUATING the effect of any intervention that influences aging requires some sort of endpoint to be measured, ideally life span. Maximum life span is the key outcome influenced primarily by interventions that act on aging and is the gold standard. Median life span can also be influenced by interventions that prevent disease, thereby squaring population survival curves without necessarily extending maximum life span. Measurement of either median or maximum life span requires the study of large populations over their lifetime, which, in long-lived species, is an insurmountable barrier. Thus clinical trials in humans are unlikely to use life span as an initial primary outcome, and some sort of surrogate outcome or biomarker of aging is essential. Consequently, the discovery of robust and accurate biomarkers of aging has become a holy grail for aging research. As yet, there is no established set of biological or clinical biomarkers of aging in animals or humans, although many have been proposed (1–6).

Various criteria for biomarkers of aging have been put forward (4,6). The underlying assumption is that any intervention that alters a biomarker of aging will, by extrapolation, also alter the aging process and maximum life span. For example the American Federation for Aging Research concluded that any useful biomarker of aging should fulfill a variety of criteria, including the following:

• It must predict the rate of aging and be a better predictor of life span than chronological age alone
• It must monitor a basic process that underlies the aging process, not the effects of disease
• It must be able to be tested repeatedly without harming the person or animal
• It must be something that works in human and in laboratory animals (3)

From a pragmatic perspective, biomarkers of aging should also be easy to measure (eg, blood tests) and change over a relatively short period of time (4).

In human clinical trials of diseases, surrogate markers and composite outcomes are well-established, if sometimes controversial, endpoints that are used to facilitate and speed up the development and testing of new pharmaceutical agents. Surrogate outcomes such as blood pressure, lipids, and hemoglobin A1c are accepted outcomes for vascular disease and diabetes mellitus, whereas composite outcomes combining death, hospitalization, acute coronary syndrome, and angioplasty are frequent in cardiovascular prevention trials. We need similar approaches to study aging interventions, although this will be much more complex than for disease-based interventions (4). In 1988, the National Institute of Aging established an extensive program to develop biomarkers of aging based on studies of mice, but biomarkers of aging that could be used as surrogates for aging were not forthcoming (4).
Some of the biomarkers of aging based on our understanding of aging biology include inflammatory markers (interleukin 6, tumor necrosis factor alpha, C-reactive protein), DNA changes (mitochondrial DNA, telomeres), and markers of oxidative stress and advanced glycation endproducts (4,6,7). Panels of clinical biomarkers (composite outcomes) that predict age and risk of death have been developed from longitudinal human studies, including anthropometry, muscle strength, serum albumin, blood pressure, forced expiratory volume (FEV1), lipoproteins, and cognitive and functional status. Such parameters might predict chronological age and risk of death, but many overlap with typical definitions of disease or disease risk factors. The -omics technologies are promising to generate novel but complicated biomarkers based on patterns of change in tissue or blood transcriptome, proteome, metabolome, microRNAs, and DNA methylation (7,8). Detailed profiling of posttranslational modification of circulating proteins (e.g., N-glycans on circulating glycoproteins such as immunoglobulins) has also generated new biomarkers of aging (9), and this approach has been promoted for future research on aging and biomarkers (8,10).

In this issue of the Journal of Gerontology, a new study of the relationship between aging and posttranslational glycosylation of IgG is reported (11). This study might prove to be a significant advance because of the strong statistical association with chronological age and plausible mechanistic contribution to age-related changes in inflammation. Krištić and colleagues (11) studied 5,117 participants ranging in age from 16 to 100 years from four different European cohorts—the Croatian island of Vis, the Croatian island of Korcula, Scottish Orkney Islands, and the TwinsUK cohort. There were complicated but strong relationships between changes in IgG glycosylation and age. The greatest impact of age was a reduction of about 50% in galactosylation. This finding had stood the test of time, having been reported in 1988 by Parekh and colleagues (12). They developed an index called GlycanAge, which combined three of the IgG glycans and explained nearly 60% of chronological age. Then they studied the relationship between age, IgG glycans, and other clinical biomarkers of aging such as anthropometric measurements, lipids, blood pressure, and FEV1. Once again, the IgG glycans proved to be strongly associated with age when these other markers were taken into account. From about 50 years of age, 71% of variance in chronological age could be predicted by a combination of glycans, systolic blood pressure, and FEV1.

As well as being a strong statistical marker of aging, glycans are of particular interest because they regulate pro- and anti-inflammatory IgG responses by influencing the binding of IgG to its various receptors. For example, the age-related reduction in IgG galactosylation will increase the proinflammatory function of IgG. This is of importance, given the key association of inflammation with aging, a process termed inflammaging by Franceschi and colleagues (13). The authors conclude with the appropriate epidemiological caveat that the direction of causality between aging and altered IgG glycosylation is uncertain. Even so, IgG glycans might prove to be significant biomarkers of aging because of both their strong statistical link with age and their plausible mechanistic link with age-related changes in inflammatory responses.

References