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Highlights From the Latest in Diabetes Research

Cellular Senescence and Aging: Implications for Both Duration and Quality of Life

A new report provides intriguing new data on the potential role of cellular senescence in aging and metabolic dysfunction. Aging is accompanied by development of chronic diseases as well as loss of function, changes in body composition, and insulin resistance. Despite these well-recognized patterns, the specific mechanisms by which aging increases risk of disease and loss of function are poorly understood. Cellular senescence, which results in accumulation of senescent cells in various tissues, is postulated to contribute to aging in humans and other organisms through unfavorable effects on tissue structure and function. If causally associated with aging-related dysfunction, cellular senescence could be a meaningful target for future therapies. Recently, Baker et al. published data from an intriguing set of experiments in progeroid mice in which a novel transgene (*INK-ATTAC*) was used to induce removal of $p16^{Ink4a}$-positive senescent cells from various tissues.

Baker's experiments yielded a number of interesting results among treated mice, including clearance of senescent cells from several tissues that often show age-related dysfunction, including adipose tissue, skeletal muscle, and eye. These experiments also suggested that ongoing removal of senescent cells delayed the onset of aging-related phenotypes such as cataracts and sarcopenia and late-life clearance inhibited progression of established pathologies. Treated mice also performed better on treadmill testing and lost less body fat, a recognized aging phenomenon in mice. Notably, other age-related changes including abnormalities in cardiac structure and function, which may occur independently of $p16^{Ink4a}$, were similar in treated and untreated animals.

The data from these experiments provide a tantalizing glimpse into the potential therapeutic implications associated with targeting the mechanisms underpinning cellular senescence and perhaps its associated metabolic dysfunction. However, it should be emphasized that these experiments were conducted in a mouse model of accelerated aging in which accumulation of senescent cells is also accelerated—a consideration that raises questions regarding how well this model reflects normal aging. Further, although phenotypes of great potential importance such as cataracts and muscle function were improved in treated animals relative to untreated ones, life span was similar across the two groups, although the latter outcome was not a central focus of these experiments. Nonetheless, these experiments may serve as proof of principle regarding the importance of cellular senescence. Given the rapid growth in the older population in the U.S. and other developing countries and the accompanying burdens associated with declining function and increasing costs, Baker's divergent results with respect to functional phenotypes and life span are a reminder of the importance of considering quality, and not just duration of life when contemplating the implications of new therapies. — *Helaine E. Resnick, PhD, MPH*

■ Baker et al. Clearance of $p16^{Ink4a}$-positive senescent cells delays ageing-associated disorders. Nature 2011;479:232–236

GAD65 Antigen Therapy Not Successful in Preserving β-Cell Function Among Patients With Newly Diagnosed Type 1 Diabetes

Less than promising results of recent clinical trials on both prevention and treatment of type 1 diabetes have led to a focus on autoantigens as a means to induce immunologic tolerance. Among the autoantigens that have been targeted in recent studies is alum-formulated GAD65 (GAD-alum). In a phase 2 study of 70 patients with type 1 diabetes, GAD-alum delivered promising results for fasting C-peptide at 30 months and stimulated C-peptide at 15 months. The same research group recently published disappointing results of its phase 3 study of GAD-alum, which followed 334 patients for 15 months.

This trial enrolled patients within 3 months of diagnosis and included three treatment groups: four doses of GAD-alum, two doses of GAD-alum and two doses of placebo, or four doses of placebo. The primary outcome was change in stimulated C-peptide between baseline and 15 months, and a number of secondary outcomes were also examined. At 15 months, there was no difference in the primary outcome between the active drug groups and the placebo group, nor were differences observed in secondary outcomes such as insulin dose or glycated hemoglobin.

The authors speculate that a number of factors could explain why results of their phase 3 trial differed so markedly from those in the phase 2 study. One explanation could be that the larger enrollment in phase 3 required involvement of a larger number of clinicians who could have introduced variability in conventional treatment. Other explanations could involve seasonality at first treatment, as well as an epidemic of influenza and accompanying vaccinations that occurred during the study period. Regardless of the reason for these disappointing results, it is clear that more work is needed to understand the viability of autoantigen treatment in type 1 diabetes. — *H.E.R.*

■ Ludvigsson et al. GAD65 antigen therapy in recently diagnosed type 1 diabetes mellitus. N Engl J Med 2012;366:433–442

Joint Associations of Physical Activity and Sedentary Behavior in Relation to Cardiometabolic Risk Factors in Children

Are there measurable benefits to physical activity even among children who are highly sedentary? Television watching, computer use, and, most recently, the growing popularity of handheld electronic devices are all on the rise among children and adolescents in the U.S. and elsewhere. These behaviors contribute in meaningful ways to development and maintenance of sedentary behaviors at young ages, and these behaviors often persist into adulthood. It has been demonstrated that daily time spent in sedentary activities increases throughout childhood into the teenage years and is higher among non-whites and among people of lower socioeconomic status and that these behaviors contribute to higher BMIs in these subgroups. It is also known that physical activity at young ages is inversely associated with cardiometabolic risk factors. A compelling new report provides a fresh look at both sedentary time and physical activity in a meta-analysis of 14 studies containing data for nearly 21,000 children aged 4–18 years. The study focused on several key risk factors including waist circumference, systolic blood pressure, fasting triglycerides, HDL cholesterol, and insulin.

Perhaps the most intriguing finding in this analysis was that the amount of time children spent in moderate to vigorous physical activity was associated with more favorable cardiometabolic profiles regardless of the amount of time the children were sedentary. Clear trends showing the beneficial impact of physical activity were observed for multiple risk factors even among children with the highest levels of sedentary behavior. Further, the authors found no association between sedentary time and these risk factors once the amount of physical activity time was considered.

The authors suggest that one public health message associated with these findings is that children should be encouraged to increase time in physical activity because it may be more beneficial to cardiometabolic health than efforts to reduce time in sedentary behaviors. Healthy People 2020 supports this general recommendation with data suggesting that current public health goals related to limiting sedentary behaviors among children are met considerably more often than those targeting physical activity. For instance, only 18% of adolescents met physical activity guidelines for aerobic physical activity, while 79% of children aged 6–14 years met the goal for limited television watching (although this goal is set at a puzzling 2 h per day). Nonetheless, it seems clear that effective strategies to increase physical activity in children are badly needed and that these strategies should be implemented regardless of the level of sedentary behavior. — H.E.R.

■ Ekelund et al. Moderate to vigorous physical activity and sedentary time and cardiometabolic risk factors in children and adolescents. JAMA 2012;307:704–712

Irisin: A Newly Described Protein Hormone That Is Induced in Exercise and Acts on Adipose Tissue

A recent article reports that a new peptide secreted from muscle may transform white fat to brown fat—a finding that may have implications for development of new therapies. Although there are clear health benefits associated with exercise in humans, the mechanisms linking exercise to improved health are poorly understood. Increased energy expenditure is a basic feature of exercise, as is the expression of PGC1-α in muscle. In mice, this transcriptional co-activator is associated with resistance of obesity and diabetes, indicating that it may secrete factors that act on other tissues. A recently published series of experiments in mice shows that PGC1-α induces expression of a number of muscle gene products, including FNDC5. In turn, the *Fndc5* gene encodes a protein for a newly identified hormone called irisin.

The published experiments showed a number of intriguing results related to the action of irisin on subcutaneous fat tissue. These included the stimulation of browning as well as expression of uncoupling protein-1, both indicative of increased metabolic activity in this tissue. Further, the data were highly consistent over more than 10 experiments and exhibited a dose-response relationship. Other experiments focused on measurement of plasma irisin levels in response to exercise in both mice and humans. Mice had a 65% increase in irisin levels after 3 weeks of exercise, and humans had a twofold increase after 10 weeks of endurance training. These increases correlated to increased mRNA levels in muscle. Finally, irisin led to improved glucose tolerance and fasting insulin among mice on a high-fat diet.

These experiments show that irisin is secreted from muscle and acts on adipose tissue by increasing thermogenic activity. Importantly, the data suggest that modest increases in plasma irisin can increase energy expenditure and improve key cardiometabolic features including weight, glucose tolerance, and insulin levels. If administered exogenously, irisin may hold promise for treatment of diabetes and obesity. — H.E.R.

■ Boström et al. A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 2012;481:463–468

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