Healthy aging: A novel therapy to reverse age-related damage

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What if we could turn back the clock on age-associated dysfunctions by using a therapy that not only treats symptoms but acts to correct the underlying pathology and restores cells to normal function? Lori A. Birder and Edwin K. Jackson from the University of Pittsburgh School of Medicine, explain how this could be a possibility

Increases in our aging population will put substantive burdens on the public health system as well as on medical and social services. Though age is a risk factor for disease, it is often overlooked in clinical practice. Many older people suffer from more than one disease, with the likelihood of having two or more conditions rising to 60% by 75 years of age, and both aging and multimorbidity contribute to frailty, which is associated with a risk of other complications. While several pharmacologic or cell-based strategies show promise for slowing the progression of several age-associated disorders, most 'mask' symptoms but do not reverse the condition or restore healthy form and function. Despite the prevalence and impact of age-related disorders on quality of life in humans, a multitude of age-related conditions continue to be undertreated simply because there are few successful therapeutic options, especially minimally invasive ones, and no preventative strategies nor known modulating interventions that reverse or delay physiologic changes. To further compound the problem, the prevalence of polypharmacy in the aged population can increase the risk of drug-drug interactions, which may complicate the diagnosis of many age-associated disorders.

Geroscience hypothesis and age-related damage

Historically, translational studies involving common chronic conditions and aging research have tended to work in isolation from each other, focusing on one single mechanism at a time. Recognition that aging represents the single largest risk factor from most chronic conditions and diseases, combined with descriptions of biological hallmarks of aging and the discovery of genetic and pharmacologic interventions capable of attenuating varied aspects of biological aging, has led to the emergence of the Geroscience Hypothesis. [(1)] Briefly, it states that the use of interventions capable of targeting varied biological hallmarks of aging (Gero therapeutics) will delay the onset and progression of multiple different chronic conditions and diseases for which aging represents a major risk factor.

Contribution of oxidative stress

Substantive evidence shows that mitochondrial dysfunction, increased oxidative stress, and production of free radicals (reactive oxygen species or ROS) are defining causes in a growing number of age-associated conditions. [(2)] Despite all the data that point to

important functions for mitochondria and oxidative stress in aging and the promise for future therapeutic interventions, there needs to be more information about whether effective treatments based on these fundamental biological properties could be developed to ameliorate multiple age-related disorders. Developing a single agent/class of agents that could effectively reverse age-related damage to multiple organ systems would be revolutionary.

The negative impact of aging on the urinary system is particularly common and severe, significantly contributing to decreased quality of life and increased healthcare costs. While the underlying causes of lower urinary tract disorders (LUTDs) in older adults have not been established, one of the most widely accepted hypotheses is that LUTDs arise owing to increased oxidative stress and associated mitochondrial dysfunction, which can generate ROS. [3] In this regard, chronic ischemia and associated oxidative stress increase with age, and accumulation of oxidative damage over time negatively affects all components of the LUT system, making the LUT system prone to LUTDs regardless of the proximal initiating cause. Despite evidence supporting oxidative damage playing an important role in multiple age-associated disorders, numerous clinical trials have failed to show the benefit of antioxidants for the prevention and/or treatment of age-related disorders.

There is emerging evidence that changes in the levels/activity of an enzyme called purine nucleoside phosphorylase (PNPase) reflect the extent and magnitude of oxidative injury and cellular damage. [4] PNPase is important for the metabolism of ‘tissue-protective’ purine metabolites to ‘tissue-damaging’ free radical metabolites. It helps to maintain immune function, which is impaired with age, inflammation, and injury. A decrease in ‘tissue protective’ purines have been reported in COVID-19 patients with acute kidney injury (AKI),[5] offering further support that abnormally low levels of protective purines may not only contribute to AKI, but very likely a broad range of disorders. For example, we showed that ‘redirecting the purine metabolism’ in the urinary bladder using 8-aminoguanine (8-AG), an inhibitor of PNPase, thereby increasing uro-protective and decreasing uro-damaging purine metabolites and other pleiotropic effects, exhibits beneficial effects on the LUT by reversing age-related changes in both bladder structure and function. [6, 7]

Our preclinical studies were performed in rats nearing the end of their lives who had already developed severe bladder pathologies that were unlikely to be reversed by any treatment. However, PNPase inhibition completely reversed all of the molecular, cellular, and functional bladder abnormalities associated with aging.

Opportunities for the future in tackling age-related damage

What differentiates our therapy from many others is the emphasis on slowing aging but also REVERSING aging (i.e., restoring organ form and function). Though further evidence of safety and efficacy is needed, PNPase inhibitors could offer an effective pharmacologic treatment approach- either alone or as an adjunct to current treatments, which could lead to a reduction in the dose of a monotherapy, reducing the risk of side effects. This could

result in better outcomes (improving efficacy and tolerability) for age-associated dysfunctions. Our revolutionary findings support the use of 8-AG, a PNPase inhibitor in restoring age- related (and chronic pain) conditions in cardiovascular, genitourinary, and ocular dysfunction in addition to peripheral neuropathies [6-9]. Therapies that could slow the average age- associated decline in organ structure and function would address an unmet need of the highest order and would have the greatest impact on human health span/lifespan.

In pre-modern societies, most died of infectious diseases or starvation at a young age; indeed, aging was a luxury afforded to the lucky few. Because of scientific advances, most individuals in modern societies can expect a relatively generous lifespan. However, this gift comes with a price. That price is the inevitable burden of pain, suffering, disability, and loss of independence that accompanies the aging process. Our overarching goal is to reduce the price of aging. If we succeed, our findings will make a difference to all of us because the transformation from aging with pain/disability/loss of dignity to aging with comfort/ability/ independence would be amazing.

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