p16INK4a, NAD$^+$ and sestrins: new targets for combating aging-related chronic illness?

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Abstract

Aging-related chronic illness is a price we have to pay to live longer. Prevalent among the oldest old, the condition limits their functional independence and also aggravates the course of several age-related chronic diseases. Thus, the search is on for efficient therapies that will mitigate age-related pathologies. In this manuscript we point out the potential clinical implications of recent provocative basic research in the field. New possible targets have been recently discovered, are clearly involved in age-related pathologies and might benefit the treatment of other age-related conditions, particularly metabolic diseases.

Keywords: Sarcopenia, senescence; mitochondria; homeostasis.
The functional independence of the most rapidly expanding segment of our population, the ‘oldest old’, is directly dependent on muscle fitness. By the age of 80 years, over 40% of muscle mass is lost and, in the oldest old, sarcopenia is prevalent. This condition leads to a dramatic loss of muscle mass/function and to a gait speed <1 meter/second causing frailty syndrome and disability. The economic burden of sarcopenia to the US health care system is over 18 billion dollars/year. Researchers have therefore turned their attention to identifying the biological hallmarks of aging sarcopenia. Such indicators would be able to predict the functional capacity of the elderly and be candidate targets for drug rejuvenating therapies.

A recently advocated hallmark of muscle aging is altered mitochondrial homeostasis through reduced sirtuin 1 (SIRT1) activity induced by low nicotinamide adenine dinucleotide (NAD\(^+\)) levels. A depleted NAD\(^+\) pool could be the result of both the diminished NAD\(^+\) synthesis and increased NAD\(^+\) consumption that occurs with age (Gomes et al., 2014). In effect, these authors determined that age-related mitochondrial dysfunction is not the consequence of irreparable damage to macromolecules (Gomes et al., 2014). Thus, treatment of mice with NMN (an NAD\(^+\) precursor) can restore NAD\(^+\) levels and markers of mitochondrial function that decline with age, reversing muscle mitochondrial senescence (Prolla and Denu, 2014). However, NMN has proven unable to reverse loss of muscle strength and yet a non-pharmacological human lifestyle intervention such as exercise (especially resistance exercise) can achieve muscle strength gains and functional independence in elderly subjects.

Another potential biomarker arising from recent animal research is the p16INK4a tumor suppressor. In geriatric mice, satellite cells lose their quiescent state owing to deregulation of p16INK4a, whereas repressing p16INK4a restores muscle regenerative capacity (Sousa-Victor et al., 2014). It is also known that p16INK4a expression increases with age, and its greater expression has been linked to increased subject attrition (Tsygankov et al., 2009). Moreover, recent evidence suggests that p16INK4a expression is upregulated by gerontogenic behaviors such as tobacco use and physical inactivity, pointing to a critical role in age-related diseases (Song et al., 2010).

Sestrins are a third recently discovered hallmark of aging sarcopenia. Mammalian cells express sestrins (Sesn1, Sesn2, and Sesn3) in response to stress including DNA damage, oxidative stress and hypoxia. Sestrins have antioxidant functions and can inhibit the activity of the mammalian target of rapamycin complex 1 (mTORC1) through activation of AMP-dependent protein kinase (AMPK) (Lee et al.,
2013). Interestingly, sestrins prevent sarcopenia, insulin resistance, diabetes and obesity. In addition, these small proteins extend both lifespan and healthspan through activation of AMPK, suppression of mTORC1, and stimulation of autophagic signaling (Lee et al., 2013). We recently proposed a possible role of the antioxidant and AMPK-modulating functions of sestrins in the benefits produced by exercise in older subjects, (Sanchis-Gomar, 2013).

As an essential step for the prevention of aging-related diseases, and specifically, sarcopenia, much basic research is needed on the main cellular hallmarks of muscle senescence and how they can be targeted by drug or lifestyle interventions. In addition, our increasing life expectancy will determine a need to identify a greater number of targets to combat aging-related chronic illness.

**Conflicts of Interests:** The authors declare no conflict of interest.

**References**


