Determinants of Frailty and Longevity: Are They the Same Ones?

Leocadio Rodríguez Mañas

Both longevity and frailty share some common facts, with loss of the functional reserve being one of the most relevant [1]. However, although it looks that longevity and frailty share some causes that act by mechanisms similar to those being involved in both longevity and frailty, other causes produce beneficial effects prolonging longevity but increasing the risk of frailty, and, finally, some exclusive causes operate independently on different mechanisms.

During life, the decline in function has an underlying rate of 0.5% per year in all systems, where most data are available for those aged 30–70 years, although data from the Baltimore Longitudinal Study (measuring peak treadmill oxygen consumption) suggest that this rate can be accelerated with advancing age, reaching rates of 2% per year in the 70s and beyond [2]. Due to intrinsic aging and nonsusceptibility to changes (including physical activity during leisure time), this general, basal rate makes it unlikely to cross the line of 30% with respect to the remaining function, which determines the presence of frailty or disability. But this basal rate can be accelerated under different extrinsic circumstances with a rate ranging from a mean of 1% per week to 2% per year. These different rates have a high interindividual variability, being one of the main factors contributing to the high phenotypic heterogeneity that is typical in older people.

Nine factors have been involved in determining longevity [3]. Four of them are the 'primary hallmarks' of aging causing the original damage: genomic instability, telomere attrition, epigenetic alterations, and loss of proteostasis. The other three, the so-called 'antagonistic hallmarks' are deregulated nutrient sensing, mitochondrial dysfunction, and cellular senescence. Finally, the last two of the nine factors will be the final effectors responsible for the phenotypic changes in aging: stem cell exhaustion and altered intercellular communication, which are affected by changes in immune and inflammatory responses (inflammaging) and the endocrine system.

Table 1. Relationships between different factors and longevity/inflammation

	Longevity	Frailty
Genetic factors	Associated	Associated (±)
Epigenetic factors	Associated	NR
Cellular senescence	Associated	NR
Mitoch. dysfunction	Associated (–)	Associated (–)
Inflammation	Associated (–)	Associated (–)
IIS pathway	Associated (–)	Associated (+)
Testosterone	Associated (±)	Associated (+)
Estradiol	Associated (+)	Associated (4)
Protein glycosylation	Not relevant	Associated

IIS = Insulin/insulin-like growth factor-1 signaling; regarding longevity: + = higher levels increase the life span; – = higher levels decrease the life span; regarding frailty: + = higher levels protect against frailty; – = higher levels favor frailty.

The loss of functional capacity and functional reserve that is characteristic of frailty is mainly due to changes in two systems: hormonal dysregulation and inflammation, which, in turn, can be modulated by both genetic and environmental factors. Frailty has been associated with several traditional markers of inflammation [4] (interleukin-6, C-reactive protein, tumor necrosis factor-a, fibrinogen, D-dimer, and leukocytes, for example). The role of the adipose tissue in the origin of this low-grade inflammatory status seems to be predominant. Although the relationship between adipose and visceral adipose tissue has been mainly established, one of the changes in the body composition during the aging process is a progressive infiltration of skeletal muscles by adipose tissue, with metabolic characteristics of this adipose tissue being similar to those of the visceral adipose tissue.

Frailty is associated with an impairment in different anabolic hormones. It is in the field of hormones where the disparate effects on longevity and frailty are probably more relevant. There are three main groups of hormones involved in frailty: growth hormone/insulin-like growing factor-1 and insulin, sexual hormones (testosterone and estradiol), and cortisol/dehydroepiandrosterone [5].

In summary, longevity and frailty share some of their underlying mechanisms. This fact may explain why they are closely related, and the association between advanced age and a higher prevalence of frailty. At the same time, longevity and frailty differ in some characteristics (table 1). First, while aging/longevity is a universal and intrinsic phenomenon, frailty is modified by external factors and has its main impact on four organs. Second, some factors that prolong longevity (favorable effect

on the amount of life) increase the risk of frailty (unfavorable effect on the quality of life), while others protecting from frailty shorten life expectancy.

References

1 Fried LP, Ferrucci L, Darer J, et al: Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci 2004;59:255–263.

2 Fleg JL, Morrell CH, Bos AG, et al: Accelerated longitudinal decline of aerobic capacity in healthy older adults. Circulation 2005;112:674–682.

3 López-Otín C, Blasco MA, Partridge L, et al: The hallmarks of aging. Cell 2013;153:1194–1217.

4 Bandeen-Roche K, Walston JD, Huang Y, et al: Measuring systemic inflammatory regulation in older adults: evidence and utility. Rejuvenation Res 2009;12:403–410.

5 Lamberts SW, van den Beld AW, van der Lely AJ: The endocrinology of aging. Science 1997;278:419–424.