
A Summary of the Biological Basis of Frailty

Roger A. Fielding

Nutrition, Exercise Physiology and Sarcopenia Laboratory, Jean Mayer US Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, MA, USA

Abstract

Frailty has been defined as a geriatric syndrome that is characterized by a reduction in the physiological reserve required for an individual to respond to endogenous and exogenous stressors. Using a discrete definition of frailty that includes sedentariness, involuntary weight loss, fatigue, poor muscle strength, and slow gait speed, 'frailty' has been associated with increased disability, postsurgical complications, and increased mortality. Despite the strong associations between frailty and subsequent poor outcomes, limited attention to this common geriatric condition has been paid in clinical settings. A more fundamental basic understanding of the biological factors that contribute to the frailty phenotype has begun to emerge. Multiple underlying biological factors such as dysregulation of inflammatory processes, genomic instability, oxidative stress, mitochondrial dysfunction, and cellular senescence appear to contribute to the clinical presentation of frailty. This chapter summarizes the papers presented on the biological basis of frailty from the 83rd Nestlé Nutrition Institute Workshop on 'Frailty, Pathophysiology, Phenotype and Patient Care' held in Barcelona, Spain, in March 2014.

© 2015 Nestec Ltd., Vevey/S. Karger AG, Basel

Introduction

The demographic shift in the average age of the population worldwide mandates that careful attention be paid to the nutritional and health needs of all segments of our aging society. Well-defined changes in body composition

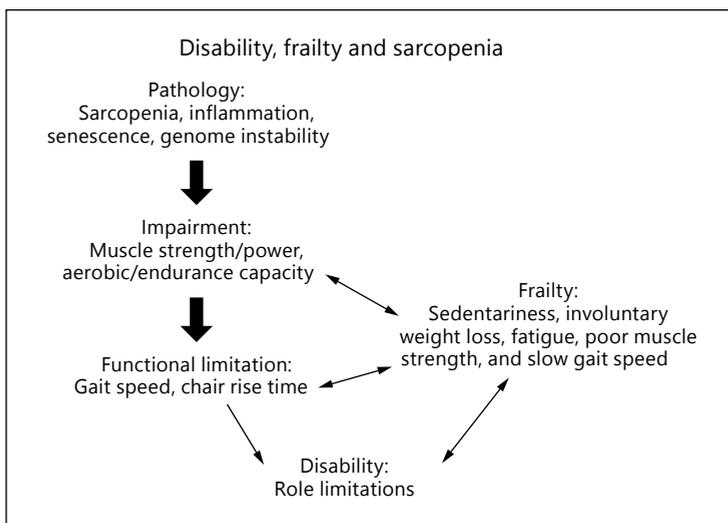


Fig. 1. Relationship between frailty, sarcopenia, and age-associated disability.

occur with advancing age. Characteristic of this change is the age-associated decline in skeletal muscle mass and function (sarcopenia). Sarcopenia has been linked to declines in physical function, loss of independence, and mortality. The functional declines associated with sarcopenia are factors that contribute to the syndrome of frailty with advancing age (fig. 1). Frailty has been operationalized as a geriatric syndrome that is characterized by a reduction in the physiological reserve required for an individual to respond to endogenous and exogenous stressors [1]. Using a discrete definition of frailty that includes sedentariness, involuntary weight loss, fatigue, poor muscle strength, and slow gait speed, Fried et al. [1] have been able to associate states of frailty with increased disability, postsurgical complications, and increased mortality. Recent work in this area has focused on the underlying biological mechanisms associated with the phenotype of frailty and the components of the frailty syndrome.

The conceptual basis for the clinical phenotype of frailty has coalesced into five distinct features including sedentary lifestyle, involuntary weight loss, muscle weakness, fatigue, and slow gait speed [1]. Hypotheses about the cellular alterations that drive this syndrome have focused on changes in the proinflammatory environment, altered hypothalamic-pituitary axis functioning, increased sympathetic nervous system activity, and increased renin-angiotensin system activation [2]. These systemic changes appear to be driving intracellular regulatory systems related to mitophagy/autophagy, apoptosis, senescence,

mitochondrial dysfunction, and epigenetic modifications. Recent work has focused on developing animal models that best reflect the frailty phenotype. Among these, the interleukin-10^{-/-} transgenic mouse model has emerged as a promising model of human frailty [3]. Future studies will require additional model systems to elucidate the underlying mechanisms driving frailty with the ultimate goal being the successful development of therapeutics for the prevention or treatment of frailty.

Cellular senescence, the process by which cells lose the ability to divide and impart damaging secretory products to neighboring cells, the senescence-associated secretory phenotype, has been implicated in age-related chronic disease and aspects of frailty. While cellular senescence may be an important anticancer defense during growth and development, the accumulation of senescent cells in tissues during aging has resultant negative consequences, including increased inflammatory burden, functional changes, and pathology. A key feature of cellular senescence in relation to age-related chronic diseases and frailty is the secretion of a number of proinflammatory cytokines, chemokines, matrix remodeling proteases, and growth factors (the senescence-associated secretory phenotype) [4]. With the development of model systems that allow for the manipulation of senescent cells [5] to determine the role of cell senescence in frailty, the development of targeted therapeutics for this process is on the horizon [6].

Genomic instability refers to the high frequency of mutations and deletions within the genome (both nuclear and mitochondrial DNA) caused by DNA damage and inefficient repair [7]. Evidence for a role of increased reactive oxygen species, altered intracellular calcium homeostasis, and iron dysregulation in advancing age has been proposed to induce age-related alterations in nuclear and mitochondrial DNA and may play a role in frailty.

Finally, questions have arisen about the distinction between cellular mechanisms associated with frailty and those specifically related to life span or longevity. Longevity appears to be controlled by a combination of genetic and epigenetic factors, nutrient-sensing systems, IGF-1 signaling, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, inflammation, and other hormonal axes [8], whereas frailty appears to be controlled by systemic inflammation and key regulatory hormones [9].

In summary, a consolidation of the components underlying frailty, the development of powerful biological tools in model systems to evaluate mechanisms, and the continuing approach to target therapeutics have pushed knowledge on the cause and treatment for the frailty syndrome to the forefront. Promising innovative therapies loom on the horizon and will do much to address the largely unmet clinical need of frailty in our aging society.

Acknowledgments

This research was supported by the National Institute on Aging (grant No. AG18844) and based upon work supported by the US Department of Agriculture (Agreement No. 58-1950-4-003). Any opinions, findings, conclusion, or recommendations expressed in this publication are those of the author and do not necessarily reflect the view of the US Department of Agriculture. This research was also supported by the Boston Claude D. Pepper Older Americans Independence Center (1P30AG031679) and the Boston Rehabilitation Outcomes Center (9R24HD065688).

Disclosure Statement

The author declares receipt of consulting payments, honoraria and research support from Nestlé Inc.

References

- 1 Fried LP, Tangen CM, Walston J, et al: Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146–M156.
- 2 Walston J, Hadley EC, Ferrucci L, et al: Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. *J Am Geriatr Soc* 2006;54:991–1001.
- 3 Walston J, Fedarko N, Yang H, et al: The physical and biological characterization of a frail mouse model. *J Gerontol A Biol Sci Med Sci* 2008;63:391–398.
- 4 Tchkonja T, Zhu Y, van Deursen J, et al: Cellular senescence and the senescent secretory phenotype: therapeutic opportunities. *J Clin Invest* 2013;123:966–972.
- 5 Baker DJ, Wijshake T, Tchkonja T, et al: Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. *Nature* 2011;479:232–236.
- 6 Naylor RM, Baker DJ, van Deursen JM: Senescent cells: a novel therapeutic target for aging and age-related diseases. *Clin Pharmacol Ther* 2013;93:105–116.
- 7 Vijg J, Suh Y: Genome instability and aging. *Annu Rev Physiol* 2013;75:645–668.
- 8 Lopez-Otin C, Blasco MA, Partridge L, et al: The hallmarks of aging. *Cell* 2013;153:1194–1217.
- 9 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.