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Review

Frailty and the homeostatic network

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Abstract. Trajectories of health and functioning with age show extreme variability among different individuals. In frail, older persons the decline in functional reserve is accelerated and compensatory mechanisms start failing, with high risk of homeostasis disruption and consequent negative health outcomes. Frailty is currently conceptualized as an age-related alteration in physiology and pathology that results into a typical constellation of signs and symptoms. Although current attempts to identify frail, older individuals for clinical purposes is based on measures of mobility and motor performance, candidate biological markers that may be specific of the frailty syndrome start to emerge in the literature. Different theories have been drawn to describe the interaction of aging process and loss of ability in performance. One of these hypothesis is based on the progressive dysregulation that occur with age in the homeostatic network and the less efficiency and efficacy in its vital mechanism that allows at all levels integration, from mitochondrial function to societal and community adaptations. (www.actabiomedica.it)

Key words: Frailty, disability, homeostatic network

Frailty, a condition highly prevalent in the geriatric population, can be defined a state of vulnerability to stressors as a result from the difficulty in maintaining homeostasis in the face of perturbations, due to decreased physiologic reserves (1). It correlates with many adverse health outcomes, including disability, dependency, falls, hospitalization, need for long-term care and mortality (2).

Aging has been conceptualized as declining efficiency of the mechanisms that maintain the homeostatic equilibrium, which is continuously challenged by destabilizing events (3, 4).

Trajectories of health and functioning with age are exemplified by the curves shown in Figure 1. "Performance" can be divided into three meaningful levels that, in the figure, are shown with different shades of red. The first is the area of "full performance", characteristic of persons who because of high functional reserve are able to face environmental challenges (e.g.: diseases, traumas, life events) that may potentially destabilize the biologic al homeostasis. The second is the area of "frailty", which is characterized by high degree of susceptibility to external and internal changes, probably due to the exhaustion of functional reserve and compensatory mechanisms. Persons in this area are at high risk of homeostasis disruption and consequent development of negative health outcomes, including disability and death. Finally, we have the area of "disability", characteristic of persons who for a number of

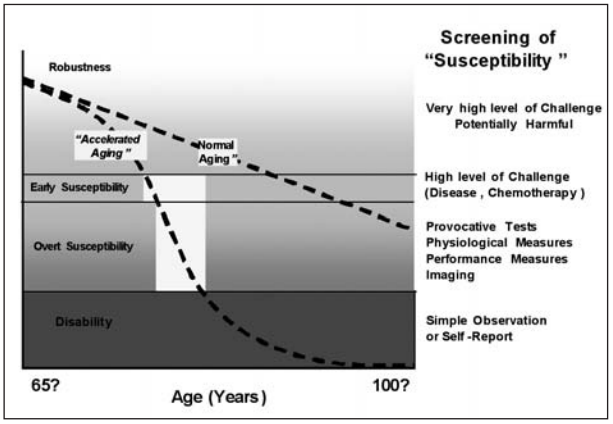

Figure 1. Aging Paradigm "The Speed of Decline"

different reasons have lost their ability to conduct an autonomous life and require the help of another persons to perform even the simplest self-care activities of daily living. In the "normal aging" the decline is almost completely contained within the area of "full performance" and therefore it does not influence substantially the ability to enjoy a satisfactory and independent life. Unfortunately, this trajectory is representative of only a small portion of the elderly population. In fact, in most persons, the decline of "performance" crosses the threshold of disability some years prior to death, and sometime even at relatively "younger" ages. In some instances, acute conditions such as stroke or hip fracture cause a sudden drop from the area of full functioning to the area of disability in Activities of Daily Living (ADL). However, in about half of older persons, disability develops progressively and the trajectory of performance passes through the intermediate stage of frailty, which in Figure 1 is shown as a time-window between the time at which the trajectory leaves the area of full performance and before it enters into the area of ADL disability. Several lines of research indicate that persons who are in this area of transition are at high risk of disability and, therefore, they are also those who can profit the most from interventions of disability prevention. Analogously, there is general agreement evidence that frailty is a physiological syndrome including an excessive reduction of lean body mass, a reduction in walking performance and poor endurance associated with a perception of exhaustion and fatigue (2). Although other features, such as loss of appetite, disturbed energy metabolism and impairment of immunologic surveillance have been described as important, there is evidence that the core target of the frailty syndrome is motor organization, and specifically the muscular and the nervous systems. An appealing hypothesis is that disease, disuse and aging "per se" trigger a mechanism that impoverishes the redundancy of muscular and nervous backup systems and, when the damage goes beyond the threshold of possible compensation, leads to a measurable decline of motor performance. To some extent, once this mechanism is activated, its progression becomes independent of the nature and the persistence of the triggering cause, and its consequences follow a common pathway, negatively influence muscle and nerve function. According to this hypothesis, our best chance of screening for the frailty syndrome is based on measures of the physiologic subsystems that are related to mobility and motor performance (6). Indeed, there is strong evidence that poor performance in lower extremity function is a strong predictor of a number of negative outcomes, including ADL disability and mobility disability (7), hospitalization (8), nursing home admission (9) and death.

a. The Homeostatic network and the InCHIANTI paradigm

Aging may be conceptualized as a progressive dysregulation of our homeostatic network, and that life is maintained owing to the incredible adaptability and resiliency that the network allows at all levels of integration, from mitochondrial function to societal and community adaptations. There is evidence that, with aging, this homeostatic network undergoes a progressive simplification and tends to generate responses that are more stereotypic, more costly, and less effective (3). We are also starting to realize that the dysfunction of the homeostatic network can be detrimental to health. If the dysfunction of the homeostatic network is the primary cause of increased susceptibility to disease, then the distinction between aging and pathology, while still conceptually valid, is almost impossible to detect empirically and certainly cannot be summarized by a few single measures. Perhaps this is why, in spite of considerable resources, the search for unique "biomarkers of aging" has so far been extremely disappointing. Studies have demonstrated that performance in mobility is a marker of health status superior to any other biomedical measure and one of the main determinants of quality of life in old age. In the InCHIANTI Study, slow walking speed (<0.8 m/s) was as a strong predictor of mortality as a diagnosis of malignant cancer (Figure 2). Studies have also shown that poor lower extremity performance is a robust predictor of multiple negative health outcomes, including disability, health care resources utilization, nursing home admission, and mortality (7-9). Mobility may be interpreted as an overall measure of homeostatic stability, and understanding the causes of mobility disability may help explain the homeostatic disruption that occurs with aging. These conceptualizations have

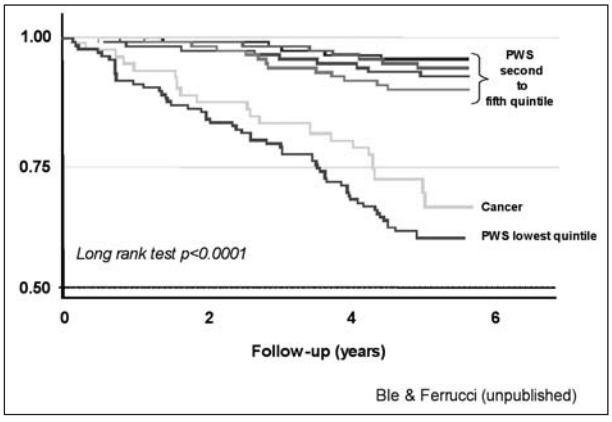

Figure 2. Preferred Walking Speed Predicts Mortality

been translated in the InCHIANTI Study (6) paradigm illustrated in Figure 3. On the right side of the figure is mobility, the key outcome measure. In the middle are physiological domains that are relevant for mobility. In brief, the central nervous system generates the motivation for mobility and also creates, refines, and provides feedback to motor programs wired through the peripheral nervous system. Muscles are effectors that move bones and joints. Mobility requires that energy be generated, transported, and delivered locally, and that somatosensory systems provide continuous feedback from the environment. The hypothesis underlying this paradigm is that mobility problems in older persons result from impairment in multiple physiological domains, even when the clinical presentation suggests one precipitating cause. On the left side of the figure is a first attempt to identify the essential elements of the homeostatic network. We have hypothesized that the aging process affects multiple physiological systems in parallel (harmonically) because the signalling network that maintains a stable homeostasis and adequate distribution/utilization of energy becomes progressively less efficient and less able to adapt to stress with aging. The primary elements required for energy generation are provided by nutrition (in this context, oxygen is considered a nutrient). Most energy expenditure is accounted for by resting metabolic rate and physical activity. The production of energy during aerobic metabolism generates reactive oxygen species (ROS; oxidative stress) that are scavenged by antioxidant mechanisms. A dynamic stability of the internal environment is maintained by the combined effects of hormones and the autonomic nervous system. Finally, the integrity of the "self" is maintained by the immune system through inflammatory processes. Although it is useful to discuss these homeostatic systems separately, they appear to belong to the same signalling network and function in a very integrated way.

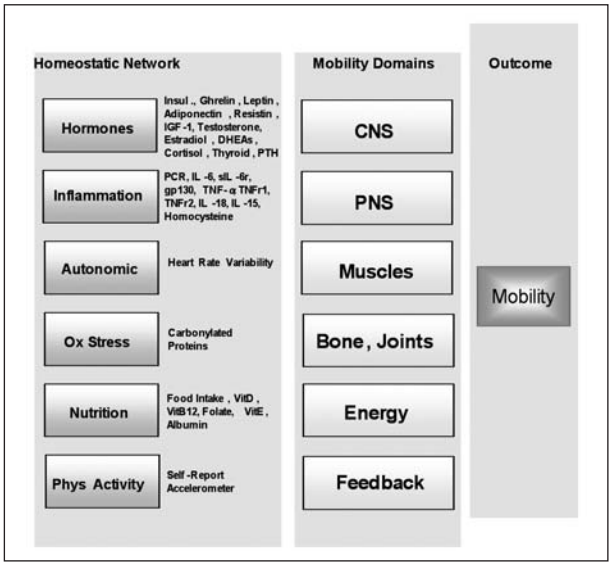

Figure 3. The Homeostatic Network in the InCHIANTI

b. The resting metabolic rate

The idea that resting metabolic rate and longevity are related was the basis for the Pearl's "rate of living theory", a theory about the aging process that has never been totally rejected. (10). The minimum amount of energy required to maintain life in a resting condition and thermal equilibrium is defined as Basal Metabolic Rate (11). This is the amount of energy (BMR) needed simply to maintain the human machine in an homeostatic equilibrium: for the sodium potassium pump, circulation of the blood, constant filtration in the kidney, millions and millions of synapses firing at the same time in the brain. Such energy is generated in terms of ATP molecules, but because most of the energetic metabolism is aerobic, it can be operationally assessed as MV02max. The BMR is maximum in the first years of life, perhaps because of massive anabolic processes related to growing and de-

velopment, and it declines at a fast rate up to the age of 20, and then declines more slowly for the rest of life. Aged-changes in body composition, and aged-decline on physical activity strongly affect BMR but aging is associated with no significant decline in BMR. The evidence that inadequately high BMR is detrimental has been recently confirmed by studies in patients with stroke and affected by chronic respiratory conditions. As a consequence, some researchers have proposed that factors influencing basal metabolic rate are not limited to physiological factors but include also pathological components as well. On top of the "theoretical minimum requirement for homeostasis", which is a function of age, sex, body composition and physical activity, we need to consider, especially in older person, an extra-quota of energy required to balance the unstable homeostasis due to pathology. This extra energy can be defined as "homeostatic effort" and it is believed to predict mortality. Above the energy for minimal homeostatic requirements and the "homeostatic effort", most of the remaining energy is used for activities, both cognitive and physical. This amount of energy may be highly diminished if the "homeostatic effort" is high. Within the range of energy that is used for physical and cognitive activities, with increasing workload, the individual starts feeling a certain level of effort, which is the subjective equivalent of fatigue. This threshold of fatigue is set by a number of still unknown factors, which certainly include biological (inflammation, oxidative stress, hormones, anabolic metabolism), psychological, and physiological factors, and also the efficiency of movement (or, analogously, the efficiency of thinking). Whatever factors affect this threshold, whether the threshold is low or high affects substantially how high is our usual level of physical activity of the individual in daily life. If the threshold of fatigue is low (or it is reached with small workload because the "homeostatic effort" is high to start with) the behaviour of the individual is likely to be sedentary. On the contrary, if a high level of workload can be handled without much feeling of fatigue, then the individual is likely to be physically active in daily life. Because the level of physical activity affects fitness, in the long term it may also reduce the total amount of energy that can be generated and, perhaps, may also affect "fatigue threshold", triggering a vicious cycle that leads to progressive, accelerated decline in physical function. In this model, an active lifestyle is the best preventive strategy to frailty. Thus fatigue is the causal link between energetic metabolism and behaviour. Understanding factors that modulate fatigue at sub-maximal workload is essential to understanding the process that leads to frailty in elderly.

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