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Review

Biology of frailty: Modulation of ageing genes and its importance to prevent age-associated loss of function

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ABSTRACT

Frailty is associated with loss of functional reserve as well as with the prediction of adverse events in the old population. The traditional criteria of frailty are based on five physical determinations describing the Cardiovascular Health Study. We propose that to increase the predictive capacity of the established clinical indices, biologic and genetic markers of frailty should be taken into consideration. In recent times, research for biological markers of frailty has gained impetus. Finding a biological marker with diagnostic and prognostic capacity would be a major milestone to identify frailty, and more interesting, pre-frailty status. In the first section of the manuscript, we review the available biomarkers that help to monitor and prevent the evolution and the efficacy of interventions to delay the onset of frailty and to prevent its progression to incapacity. We also discuss the contribution of genetics in frailty. There are scientific bases that support that genetics is going to influence frailty, although environmental factors probably will have the highest contribution. We review the SNPs of the genes associated with frailty and classified them, taking into account the pathway in which they are involved. We also highlight the importance of longevity genes and its possible relation with frailty, citing centenarians who reach a very old age as an example of successful ageing. .

Finally, the reversibility of frailty is discussed. It can potentially be treated with nutritional or pharmacological interventions. However, physical exercise seems to be the most effective and popular strategy to treat and prevent frailty. The last section of the manuscript is devoted to explaining the recommendations on the appropriate design of an exercise protocol to maximize its beneficial effects in a population of frail individuals.

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1. The biology of frailty

1.1. The concept of frailty

Frailty is a new physiopathological concept that has gained relevance in recent times especially as it is very easily applicable to clinical practice. Frailty is an important prognostic criterion for difficult therapeutic decisions, especially in the surgical and oncological fields associated with ageing (Hamaker et al., 2012). There has been a consensus recently on the definition of frailty, emphasizing the progressive relationship with disability (Rodriguez-Manas et al., 2013). Frailty is associated with loss of functional reserve as well as with the prediction of adverse events in the older population. Frailty can be explained in part by the genetic load of individuals, but this is associated with the well-known variability of the phenotypes of frailty (Dato et al., 2012).

The traditional criteria of frailty, as first published by Fried, are based on five physical determinations describing the Cardiovascular Health Study: unintended weight loss, muscle weakness, fatigue, low levels of activity and slow and/or unsteady gait (Fried et al., 2001). Respectively, scores greater than or equal to 3, 1–2, or 0 indicate whether a person is frail, pre-frail or non-frail, respectively. This is the most frequently used index and its prognostic capacity has been extensively validated (Ensrud et al., 2009). There are other indices of frailty; for instance, that of Rockwood (Rockwood and Mitnitski, 2007) is more complex and less used than that of Fried. There is a third model that combines both previous models (Fried's and Rockwood's), in which physical symptoms, unsteady gait and the impossibility of climbing stairs, loss of weight and the presence of established clinical diseases are considered (Pal et al., 2010). A fourth model, described in the study of osteoporotic fractures, has a similar predictive strength as the classical Fried values (Kiely et al., 2009). Inclusion of processes such as the cognitive alteration or body mass index increases predictive and prognostic capacity over the classical definition. In fact, we propose that to increase the predictive capacity of the established clinical indices, biologic and genetic markers of frailty should be taken into consideration.

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