

## Commentary

# Insights into the molecular mechanisms of stress and inflammation in ageing and frailty of the elderly

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## Abstract

Frailty is a natural state of physical, cognitive and mental decline that is expected in the elderly. The role of inflammation in the pathogenesis of frailty has been hypothesized, and so far many studies have been performed in order to understand the mechanism of action underlying this association. Recent studies support this hypothesis and show a clear association between inflammation, frailty, and age-related disease. Chronic inflammation is key pathophysiologic process that contributes to the frailty directly and indirectly through other intermediate physiologic systems, such as the

musculoskeletal, endocrine, and hematologic systems. The complex multifactorial etiologies of frailty also include obesity and other age-related specific diseases. Herein, we investigate the link between chronic inflammation and frailty of the older people. In particular, we present an up-to-date review of the role of cytokines, interleukins, cardiovascular abnormalities, chronic high blood pressure, hyperlipidemia and diabetes in relation to the severity of frailty in the elderly.

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Frailty is a syndrome characterized by diminished strength, endurance and reduced physiological function that increases an individual's vulnerability for developing increased dependency. Frailty is also related to multiple pathologies: weight loss, and/or fatigue, weakness, low activity, slow motor performance, as well as balance and gait abnormalities. Frail elderly are more vulnerable to stressors and major health care implications, which in turn has an impact on the planning and delivery of health and social services. Frailty together with functional decline and disability are common conditions among older

people, and are increasing with ageing. However, frailty is a dynamic and not an irreversible process; it seems preventable, may be delayed, or even reversed (Clegg *et al.* 2013, Xue 2011). The aim of this report is to examine the influence of inflammation on our health.

Inflammation is our natural mechanism of maintaining our body's homeostasis (Kotas & Medzhitov 2015). The occurrence of inflammation is inextricably combined with the exposure of our inner systems to potentially harmful microorganisms, known as pathogens. However, in certain cases this

mechanism falsely targets well-functioning cells of the body, in a situation associated to the autoimmune syndromes.

Firstly, triggered by the intervention of inflammatory mediators, vasodilation escalates the blood flow. Simultaneously, increased permeability of the blood vessels results in the leakage of proteins and fluid into the tissue. At this stage, it is evident that the area has become red, has increased its temperature and has become swollen. Soon after, neutrophils and macrophages take action. Neutrophils migrate outside the blood vessels and adhere first into the tissue with the assistance of chemotactic gradients, which enable them to become attached firmly onto the endothelial cells (Kim & Haynes 2012). Phagocytes have non-specific microbe affinity and efficacy and immediately act to extinguish the harmful agent by encapsulating it. Next to arrive are the macrophages, which move slower inside the blood vessel, but induce a more effective impact than their partners. During the apoptosis of neutrophils, antimicrobial substances, such as NO, OH and H<sub>2</sub>O<sub>2</sub>, are released into the blood stream destined to destroy the pathological stimuli. However, their effect is not specialized towards each specific factor, meaning that the surrounding healthy tissue may be damaged too. In parallel, this process is enhanced by a group of preformed proteins released into the plasma in an inoperative form, the complement system, which destroys the injurious factor without encapsulating it, but by creating pores on the microbe's cellular surface. However, microorganisms and particularly bacteria are able to adjust quickly to this strategy by developing an additional protective surface. In these cases, chemical factors, namely opsonins (Stuart *et al.* 2006), make contact with the macrophage and the microorganism and create a complex. C3b (member of the MAC) and CRP (C-reaction protein) belong to this category (Du Clos 2000, Merle *et al.* 2015). The procedure described above concerns cases where the human body becomes exposed to the harmful factor for the first time.

The human body is so resourceful that it has developed a method of "remembering" the different types of pathologic agents. This results to even more immediate and acute response if one of these agents enters the human body. In this situation, it is again the macrophages who initiate the process. After encapsulating the agent, they divide it into smaller protein molecules. Subsequently, each molecule gets attached to MHC II proteins and becomes exposed to the cellular surface. At this point, the CD4 cells, through a unique receptor specialized for this specific antigen come in contact with the macrophage. The connection between the two is also enhanced by the presence of other proteins found on the cell membrane, while, IL-1 and TNF are produced by the macrophages in order to fully activate the CD4 cells.

The CD4 cells then release IL-2 which leads to

the increase of their population forming clones and the activation of B cells. B cells are responsible for three major roles (Carter 2006). Firstly, they mature into plasmacytes that produce antibodies which enter the blood stream. Each antibody is genetically destined to recognize one and only particular antigen. Secondly, a part of B cells population transforms into memory B cells. Moreover, it is possible that they behave like macrophages, revealing an injurious antigen to the CD4 cell. The complex of an antibody and an antigen enables the destructive efficacy of the macrophage. Inflammation appears to be a mechanism triggered by one single incident and to be completed with the elimination of the pathogen. However, in certain cases, it may become established and persist in a particular area of the body.

Nowadays, science has progressed significantly enough to comprehend most of the extremely specific and complicated steps our body takes to protect itself. Because of this, we are able to examine how inflammation contributes, among others, to frailty. The base of the hypothesis is a linkage between high levels of cortisol and the activation of inflammation markers (Wolkow *et al.* 2015). It is believed that the incidents of chronic inflammation are responsible for the "weakening" of the individual's stamina (Slavich & Irwin 2014).

Since it has come to our realization that despite our material wealth, increased access to goods like sterilized water, safely preserved food and advanced drugs, the human population faces an even wider range of health issues seemingly relevant to a series of inflammation incidents, we ought to wonder: why is frailty so common among the population? This question derives from the simple example of the Galapagos Islands. Even though the islands' biodiversity is under threat from several sources, we cannot help but notice that the Galapagos tortoise has managed to become the longest living of its species. A probable explanation would be that the Galapagos Islands have been a secure and isolated environment in general terms. That is, stress-increasing factors have been almost eliminated and each species has been successfully adjusted to its natural habitat (Chovatiya & Medzhitov 2014).

The example described above brings us to a second question: is anxiety valued sufficiently based on the influence it imposes on our quality of living. Aiming to reach a reasonable conclusion, it is necessary to evaluate in detail each and every aspect of the majority's way of living that is potentially stress provoking. A balanced psychological status may determine the outcome of everyday life. Nevertheless, depression affects an alarming number of citizens from all social strata. Based on WHO, there are 350 million people from all age groups worldwide suffering from major depression symptoms and over 800000 of them are led to suicide each year. Depression is a mental disorder of which most frequent symptoms consist of

uncontrollable sadness, isolation from social activities, inability to concentrate, random emotional fluctuations, constant tiredness and abnormal behavior (Hidaka 2012, Kessler & Bromet 2013). Such symptoms are also intensified by solidarity -which is, in most times, a conscious personal choice-, financial and social discrepancies like bankruptcy and racism and in certain cases, the unfortunate choice of profession along with inappropriate working conditions. According to studies, depression seems to affect the female population more often than the males (Albert 2015).

Secondly, it is essential to take each person's genetic background into account. It is probable that most of the population have inherited altered biochemical paths encrypted into the DNA, resulting in, for example, the abnormally excessive production of cortisol into the blood stream or even, falsely triggering the inflammation factors after no severe threat (Wilcox 2005). This automatically leads to general inflammation incidents that target no particular pathogen. In the first case mentioned, the gene defect would be translated as a benign mass in the adrenal glands while, in the second one, the conditions referring to this situation are the autoimmune syndromes, like rheumatoid arthritis (van Vollenhoven 2016).

On the other hand, health wise, cardiovascular abnormalities in combination with chronic high blood pressure, hyperlipidemia and diabetes exhaust the resources of the human body (Marra *et al.* 2015, Reule & Drawz 2012). The simultaneous effect of the conditions mentioned may be found in a vast amount of men over the age of 45 and women over the age of 55 (women can be protected thanks to estrogens) and can also be linked with genetic predisposition (Blum & Blum 2009). Such patients are advised to receive medication for life to prevent the formation of atheromatic plaque in the blood vessels and prolong their life expectancy. Such conditions could develop into constriction of the blood vessels in the extremities, sudden ischemic and bleeding strokes, aneurisms etc. However, it is common for patients to neglect the regular visits to specialists and take no action about their condition. Unfortunately, physicians confirm that prevention could be accomplished in condition that citizens are thoroughly informed and educated about the importance of regular check-ups.

The excessive release of cortisol in the blood stream may also contribute to a generalized hormonal alteration. Automatically, the human body will start producing hormones uncontrollably and under no specific mechanisms of action (Chen *et al.* 2014). For example, CRP and PTH will increase; the first one triggering the mechanism of inflammation, while, the second one, destroying bone tissue. This may also lead to loss of appetite and malnutrition. The latter is responsible not only for metabolic rhythm abnormalities, but it can also lead to major muscle

tissue loss. It is therefore logical that major bone and muscle tissue loss will result in the so called frailty of the elderly (Clegg *et al.* 2013).

Furthermore, examining the example of the Galapagos Islands, we ought to point out that throughout history the organisms inhabiting the islands have developed unique ways of surviving (Gentile *et al.* 2009). For instance, the iguana of the Galapagos has developed the ability to dive up to 10 metres underwater and feed on sea organisms. Its capacity might be the answer to a previous shortage of food on land, or a sudden increase in the iguana's population. It is the instinct for survival that led the iguana for food underwater, a plan that proved successful and was later encrypted into the species' genome. In this situation, it is clear that there is a positive effect of stress provoking situations too, because they contribute to the progression of species.

In conclusion, taking into consideration all cases mentioned above, it is essential to determine all mechanisms that lead to frailty. Probably, the answer is in our everyday life and the decisions each individual makes for themselves. Cortisol and inflammation may become an ally to the amelioration of human race, but, they also create numerous health issues, sometimes minor, but sometimes severe, which can decrease the quality of life.

## Conflicts of interest

None.

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