

# Stress/inflammation and pai-1 as stellar processes in the aging and associated pathologies

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Decades ago Hans Hugo Bruno Selye expressed the concept of stress as a pathophysiological syndrome generated by various endogenous / exogenous harmful agents and named it as the "General Adaptation Syndrome". This concept implicitly involves a complex process of damage and specific or non-specific defence of the organism that accompanies us throughout life, especially in the aging process and the diseases associated, whose symptoms are independent of the nature of the harmful agent, representing a response to the damage as such [1-3].

The development of the individual after their conception, development and later decline phase is accompanied of processes due to stress alarms of small intensity [4-7] and it constantly produces homeostatic adaptations [8,9] through sub lethal exposures of stressors (Hormesis) [10]. At the experimental level, tensions of greater intensity, cause progressive changes in the anatomical structure and function of the different organs, as well as vascular infarcts by intravascular coagulation in the hypothalamic-pituitary-adrenal-renal (HPA) axis [11]. This brings a marked increase in PAI-1 expression in induced stress [12-16] or in the presence of any chronic/acute phase inducer, which would explain the frequency of cardiovascular-thrombotic complications in aging [17].

Aging is recognized as a substrate of risk for the accumulation of multiple diseases of chronic evolution, producers of biomarkers indicative of the alteration of different physiological mechanisms. A myriad of theories or hypotheses have been exposed to explain the aging process [18], being the theories of free radicals and genomics the most accepted ones and related as a response to stress [19-23]. Nowadays aging is summarized as a process generated by a synergistic action between two or more causes producing a progressive damage to molecules, cells, organs and systems.

Aging begins with the organic and functional decline of the organism and leads to a progressive decrease of the main cellular and extracellular antioxidant: glutathione (GSH), giving rise to the complex mechanism of oxidative stress (OS) that plays a great role in the development of aging and associated diseases.

Both chronic stress and inflammation play a key role in the onset and progression of the different chronic pathologies that frequently accompany the development of aging [24]. It is well documented that the pathophysiology of chronic disease that underlies the process of aging, involves secretion by adipose tissue (especially abdominal type,

of pro-inflammatory markers (adipokines) setting a pathophysiological crossroads that increases the risk of morbidity/mortality. Likewise, in the development of aging there is a higher concentration of pro-inflammatory cytokines in the cerebral compartment as well as peripheral [25-27].

It is well documented how the prevalence of obesity in the more developed Western countries is increasing in all age groups, even in the old age one. This is correlated with stress through the activation of the HPA axis, favouring the accumulation of fat and exerting a mild chronic and inflammatory stressing action with release of substances from adipose tissue (adipokines, cytokines, hormones ...) that alter the metabolic balance leading to the most frequent metabolic pathology that accompanies aging [28]. This originates a common denominator of complex mechanisms that acting enchainned and constitutes a pathophysiological crossroad at the systemic level as well and in the brain compartment, acquiring the ubiquitous PAI-1 (plasminogen activator inhibitor-1) gene acquiring a stellar role [29,30].

The PAI-1 is a strategic gene whose activity in both physiology and pathology represents a challenge for the student. It is well known the importance of PAI-1 as an inhibitor of plasminogen activators, t-PA and u-PA, regulating the systemic fibrinolytic mechanism in the field of thromboembolic disease, and at the level of the brain compartment regulating  $\beta$ -amiloidolysis [31]. Besides, it is of great interest the pathophysiological function developed by PAI-1 in aging and the multiple pathology associated: obesity, metabolic syndrome, type 2 diabetes, neurodegenerative pathology (mainly in Alzheimer's Disease and Parkinson's Disease), cancer (PAI-1 can be involved in the onset, progression and metastasis of some neoplasia), cardiovascular processes and thromboembolic complications. These clinical entities clearly show increased levels of PAI-1, leading some researchers to suggest the use of PAI-1 inhibitors with therapeutic purposes in those risk processes where reduction to physiological levels could be of interest [32-39].

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