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"Nothing has such power to broaden the mind as the ability to investigate systematically and truly all that comes under your observation in life".

Marcus Aurelius

(April 26th 121 - March 17th 180 - Roman Emperor and Philosopher)

To my family

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PREFACE

Aging can be defined as a multifactorial degenerative process resulting from the organism's loss of the ability to maintain homeostasis, ultimately leading to death. Aberrant hypothalamic-pituitary-adrenal (HPA) axis activity and elevated glucocorticoid (GC) levels have been associated to aging and age-related neurodegenerative pathologies. Evidence is mounting that stress and oxidative stress might act synergistically to induce or exacerbate the neuronal decay associated with aging.

$P66^{Shc}$ is an inducible redox enzyme which, when activated by stress, produces reactive oxygen species (H_2O_2) to trigger apoptosis and its deletion has been shown to increase lifespan in mammals. In addition, a role for this gene in regulating the effect of insulin on the energetic metabolism in mice has been recently described. A growing body of evidence has shown a redox regulation of the function of the glucocorticoid receptors as nuclear transcription factors. The $p66^{Shc}$ protein is widely expressed in the body, including GC target tissues such as pituitary and brain.

The main question addressed in this thesis was whether the interactions linking oxidative stress and the neuroendocrine system represent a crucial determinant for the aging process in $p66^{Shc-/-}$ mice. It was expected that the reduced levels of reactive oxygen species, characteristic of these long-lived subjects, would result in a more efficient regulation of the hypothalamic-pituitary-adrenal axis and hence in a delay of the aging process. With this purpose, the contribution of $p66^{Shc}$ to behavioral and neuroendocrine regulations was assessed from early post-natal life to senescence.

We show for the first time that in these mice increased longevity is associated to a slow down in physical and emotional aging, although such delay is not related to the expected interaction between oxidative stress and the neuroendocrine system. Mutant subjects are characterized by increased behavioral plasticity and lower emotionality at adulthood, in addition to a better physical performance and lower pain sensitivity at old age. These characteristics are associated with increased central levels of the neurotrophin Brain-derived neurotrophic factor, reduced markers of oxidative stress and greater resilience to stress-induced changes in the internal milieu. Notably, we show that the role of the $p66^{Shc}$ gene on lifespan in complex organisms, such as mammals, is not merely related to its oxidative stress-related function but, more in general, to effects, emerging already at adulthood and involving specific signaling pathways in the brain, related primarily to energy homeostasis and emotional behavior, which indeed emerge as important determinants of healthspan during aging. Intriguingly, metabolic and emotional aspects in the $p66^{Shc}$ mutants appear to be strictly related in a mutual interaction possibly affecting the development of the emotional phenotype in a nature-nurture fashion mediated by maternal behavior.

In conclusion our results shed light on the role of oxidative stress and metabolic signals in the context of longevity and emotionality/mood disorders. In addition, they point to $p66^{Shc}$ as a candidate genetic determinant in the trade-off between fertility and lifespan.