The functional deterioration that involves ageing clearly impacts on the quality of life of elderly population, increasing their vulnerability to illness and death. During the last decades, many experimental approaches have been employed to address functional and mechanistic questions concerning the molecular modulation of ageing and age-related diseases. However, many aspects regarding the complex interconnection between the intercellular pathways and the systemic mechanisms that regulate these processes remain to be fully elucidated. Based on the presented background, this Doctoral Thesis has aimed to evaluate the relevance of intrinsic vs. extrinsic factors implicated in ageing and age-related diseases. Hence, we have identified, using a hypothesis-driven approach, lineage-specific variants presented in the genome of two long-lived giant tortoises that may underlie their extraordinary lifespan.
These changes, which may be categorized as cell-intrinsic alterations, mainly affect processes involved in several hallmarks of ageing and cancer, such as DNA repair or immunosurveillance. Moreover, we have explored the impact of cell-extrinsic mechanisms on progeroid features and longevity, concretely evaluating the function of GDF11 in age-de-pendent decline, as well as the pivotal contribution of osteocyte-derived RANKL to the pathological alterations observed in a murine model of accelerated ageing. Finally, we have characterized the role of iron and matriptase-2 (*Tmprss6*), a negative regulator of the circulating factor hepcidin, in the establishment of an age-related metabolic disorder as obesity by using a *Tmprss6*-deficient mouse model challenged with high-fat diet. Together, this experimental work has provided biological insights aimed to clarify the regulatory cell-intrinsic and -extrinsic mechanisms that integrate the organismal communication during ageing and disease, and hopefully, may have shed some light on the development of novel therapeutic strategies designed to improve the quality of life in a gradually aged world.

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