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Title: Can the cytoprotective heat shock proteins be specifically targeted to eliminate senescent T-cells?

Immunosenescence (IS) describes the set of changes that occur in the immune system, resulting in a weakened immune function as we age. IS is characterized by increased susceptibility to infections, cancers, and age-related inflammatory diseases, all of which are associated with a higher mortality rate in the elderly. Within the cells of the immune system, an age-associated restriction of naive T-cells in conjunction with an accumulation of senescent T-cells (provoking inflammation) are key contributors to IS. While major insights into IS have been gained, the mechanisms required to counteract IS have not been unraveled. Our previous investigations have confirmed the increase with age, not only of senescent T-cells, but also of several heat shock proteins (HSPs). Moreover, we observed that training induces a decrease in the number of senescent T-cells, as well as HSP70 levels in T-cells. HSPs protect cells from various insults and favor survival. Within the current proposal we will try to understand the role of HSPs on T-cell survival during the generation and maintenance of senescent T-cells. Our primary hypothesis is that in ageing, HSPs protect cells from undergoing apoptosis - and up-regulate survival proteins - thereby promoting their potential for survival. By using ex-vivo highly purified cell populations and an in vitro model, the objectives will be: **Objective 1**- To specify the molecular mechanisms responsible for HSP expression in T-lymphocytes; **Objective 2**- To explore the protective role of HSPs in senescent T-cells. Understanding the pathway by which normal T-cells become senescent T-cells endowed with long-term persistence is key to define the mechanisms involved in immune protection and to design strategies to enhance or suppress specific immune responses. In this context, the research project in my proposal will provide novel insights into molecular mechanisms dictating the fate and nature of senescent T-cells.

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