"Immunosenescence: Searching For The Fountain Of Youth"

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The Akbar Lab has studied over the last 10 years, the regulation of telomere erosion, telomerase activation and replicative senescence of primary human T cells in vitro and *in vivo*. Through ageing grant initiatives in the UK and their participation in both national and international symposia on ageing, the Akbar group has used a primary human T cell system to investigate T cells at different stages of differentiation. Furthermore, the use of a primary T cell system in this programme of work has been used to investigate differences in signalling pathways in healthy young (<35 yrs) and old (>70 yrs) individuals increases the direct relevance of the results to ageing within the human immune system. However the current programme of work is not only designed to only investigate changes in signalling pathways, the Akbar group have developed tools and experimental systems to manipulate certain senescence-related targets to mend certain defects in senescent cells. A key ambition is therefore to both to identify and to modulate signalling pathways that become defective as T cells age/differentiate to improve their functionality.

**Abstract**

Immune function declines as we age resulting in an increased susceptibility to new infections and re-activation of latent pathogens to which we were once immune. This suggests that lifelong antigenic pressures may drive specific T lymphocytes to a functional and/or replicative end-stage, when they are no longer able to support effective immunity. This immune dysfunction is borne out in increased hospital admissions, increased health care costs and a decrease in the perceived health span of old people. This is of particular concern as human life expectancy is increasing and demographic studies predict that by 2050, >40% of the population in Europe and the USA will be over 60 years of age.

Cellular senescence has been defined as the irreversible loss of proliferative capacity despite the presence of abundant nutrients and mitogens. A central question is whether this process occurs in human T cells as they differentiate towards an end stage and whether this process leads to immune dysfunction during ageing. This is particularly relevant to humans since thymic involution in youth dictates that T cell populations have to be maintained by proliferation rather than new cellular input during ageing. However the majority of studies on cellular senescence have been performed on fibroblasts and other untransformed or transformed cell lines *in vitro*. Although the function of other other leucocyte populations may also be altered during ageing, a process commonly described as “immunosenescence”, the dysfunction is most profound in T cells. However the nature and control of cellular senescence in primary human T lymphocytes and the contribution of this process makes to decreased immunity during ageing is still unclear. However it is known that the response of T cells from aged individuals to immune activation are slower and of a lower magnitude than those of young individuals and this applies to the production of cytokines, proliferation or the induction of signalling events. In this talk I will discuss the ways by which human T cell senescence can be investigated, present data on how it is controlled and demonstrate that aspects of senescence can be reversed.