ImmunoTools *special* Award 2015

Dimitris Tampakis, BSc, MSc, PhD-student

Supervisor: Dr. Alexandra Stolzing

Regenerative Medicine, Centre for Biological Engineering,
Loughborough University
Holywell Way, Loughborough, LE11 3GR, U.K.

Epigenetic alterations upon mesenchymal stem cells aging and interaction of these aged cells with macrophages.

Biological aging is a complex process affecting most of the biological functions of an organism due to the accumulation of various stressors. The factors that contribute to aging include oxidative stresses, attrition of the telomeres and decline of DNA repair system. All these factors lead to the decrease of the regenerative potential of organs and tissues together with increased sensitivity to infections and cancer, which are prominent hallmarks of senescence (*Hayflick L, 1994*).

Not only the normal somatic cells, but also the adult stem cells are exposed to stressors during their life-span that leads to an age-dependent decrease in their number and function. Therefore, the senescence-associated loss of stemness of adult stem cells leads to the impairment of tissue repair, regeneration and homeostasis. (*Janzen et al, 2006*)

One category of adult stem cells are the mesenchymal stem cells (MSCs), also known as mesenchymal stromal cells or multipotent stromal cells. MSCs are very promising in the field of regenerative medicine and are presently tested in many clinical trials.

Regularly, extensive *in vitro* expansion of MSCs is indispensable in order to obtain cell numbers compatible with a therapeutic effect. Furthermore cells for elderly people are used in autologous stem cell therapies for the treatment of many diseases. Although, it has been identified that in vitro and in vivo aging of MSCs, causes continuous alterations in MSCs such as: proliferation rate decreases, cell size increases, differentiation potential changes, genome expression profile is altered and finally it has been demonstrated that aging clearly alters the epigenetic profile of these cells.

Epigenetics is widely known as the study of the heritable alterations in cellular phenotype or the expression of the genes that are independent of changes to the DNA sequence (*Holliday, 2006*). Epigenetic mechanisms are major factors controlling cell differentiation and development (*Cedar and Bergman, 2011*).

Progressive epigenetic changes have been observed upon aging. These alterations have been identified in various eukaryotes including human and mice (*Berdasco and Esteller, 2012*) and include alterations of DNA methylation patterns as well as of histone modifications. These

two mechanisms have been shown to play a pivotal role in senescence and aging of various types of stem cells.

My project focuses on the study of Epigenetic patterns of MSCs upon aging. Specifically, I am trying to understand what is happening to DNA methylation and Histone modification of the MSCs, as they are getting older. Furthermore, I am trying to correlate these Epigenetic alterations with changes in the gene expression upon aging. This project has great clinical relevance: if we manage to identify what are the factors in aged MSCs, playing an important role in altering gene expression that are linked to diseases such as Alzheimer's and cardiovascular diseases, we can potentially prevent these changes which may lead to the cure of these diseases. In future we are also planning to study the phagocytosis of MSC's from macrophages (MΦ) upon aging.

My Supervisor (Dr Alexandra Stolzing) and I, we are welcoming the initiative of ImmunoTools GmbH to contribute and help in our scientific research via the ImmunoTools Awards, especially in this period that funding for research is increasingly less. The ImmunoTools cytokines listed below will contribute to the study of the induction of growth and differentiation of human MSCs upon aging and will help us characterise the cells that are used in our experiments. Moreover, we will study which of these cytokines are affected as the MSCs are getting older.

Finally, part of our research will be the study of the interaction of aged MSCs having specific epigenetic alterations, with cells of our immune system and specifically with MΦ, so some of the below cytokines will contribute to the proliferation and differentiation of the MΦ.

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