Editorial

Cellular Senescence and Inflammation: Advances and Therapeutic Targets in Aging and Major Age-Related Diseases

Cellular senescence was formally described more than four decades ago when Hayflick and colleagues showed that normal cells had a limited ability to proliferate in culture. These experiments showed that human fibroblasts initially underwent robust cell division in culture but, later - after many cell doublings, cell proliferation gradually declined. The non-dividing cells remained viable for many weeks, but failed to grow despite the presence of ample space, nutrients and growth factors in the medium. After this discovery, the finding that normal cells do not indefinitely proliferate spawned two important hypotheses. The first hypothesis stemmed from the fact that many cancer cells proliferate indefinitely in culture. Cellular senescence was therefore proposed to be an anti-cancer or tumour suppressive mechanism. In this context, the senescence response was considered beneficial because it protected organisms from cancer. The second hypothesis stemmed from the fact that tissue regeneration and repair deteriorate with age. Cellular senescence was proposed to recapitulate the ageing, or loss of regenerative capacity, of cells *in vivo*. In this context, cellular senescence was considered deleterious as contributing to impair tissue renewal and function. Moreover, senescent cells can have deleterious effects on the tissue microenvironment as a consequence of the acquisition of a senescence-associated secretory phenotype (SASP) that turns senescent cells into proinflammatory cells. As a consequence, with advancing aging these cells contribute to worsening the chronic inflammatory state and to promote the appearance of some degenerative age-related diseases, including cancer. Taking into account this dual role of senescent cells, it is very difficult to understand how cellular senescence can be targeted in order to achieve a beneficial or deleterious outcome. If we consider cancer tumour-suppressor mechanism, the promotion of cell senescence could be useful to avoid the proliferation of cells bearing pro-cancer mutations but, at the same time, the SASP could promote further development of neoplastic transformation. Until recently, it was not even clear how senescent cells could contribute to aging and if the removal of senescent cells could be a target to rejuvenate aged tissues. In this context, the recent manuscript from Baker *et al.* [1] has brought new light on these aspects. By making use of an inducible elimination of p16(Ink4a)-positive senescent cells upon administration of a drug in animal models, these authors demonstrated that cellular senescence is causally implicated in generating age-related phenotypes and that removal of senescent cells can prevent or delay tissue dysfunction and extend health-span.

During this last decade, significant advances have been made in understanding the biological mechanisms of cellular senescence providing the link to investigate jointly the physiological processes governing ageing and major age-related diseases. In particular, many studies have been addressed in understanding the role played by the inflammation in cellular senescence and viceversa [2]. In this respect, some manuscripts from Salvioli *et al.* (Dept. of Exp. Pathology, University of Bologna, Italy) and Chou and Effros (Dept. of Pathology, UCLA, Los Angeles, USA) in the present special issue describe how replicative senescence is involved in the clonal exhaustion of particular immune cells and how pro-inflammatory cytokines produced by senescent cells could be involved in the development of the chronic low-grade inflammatory status that characterize the ageing status [3,4]. Indeed, persistent life-long antigenic stress upon the T-cell memory pool leads to telomere erosion and concomitant loss of proliferative capacity that is associated with functional changes (reduction in the number of naive T cells and a progressively limited T cell repertoire) within T cells during ageing [3,4]. Other papers are more addressed to review the mechanisms involved in the development of cellular senescence. Among them, Provinciali *et al*. (INRCA, Ancona, Italy) discuss the involvement of telomere shortening and of p53 functional pathways in ageing and in cancer, in which short telomeres and altered p53 function by senescent cells provoke the raising of cancer rather than to be of benefit against cancer by senescent cells [5]. Of particular interest is the emerging role played by microRNA (miRNA) in cellular senescence and in some age-related diseases, such as cardiovascular diseases (CVD), as reported and discussed by Olivieri *et al.* (Dept. of Clinical and Molecular Science, University of Ancona-Italy; and INRCA, Ancona-Italy). In this context, the importance of miRNA in endothelial and cardiac cell senescence was revealed by disrupting the function of two key enzymes (Dicer and Drosha) for miRNA biogenesis leading to CVD development. Such a molecular mechanism is related to impairment of SIRT1/p53 pathway with subsequent arrest of cell proliferation and concomitant development of resistance to apoptosis and production of pro-inflammatory cytokines by the damaged cells [6]. Therefore, the interrelationship among miRNA, proteins of the cell cycle, p53 and inflammation is fundamental for cellular senescence and the possible development of some degenerative age-related diseases, including CVD and cancer [5,6]. The interrelationships among inflammation and cellular senescence in the development of neurodegenerative disease, with a particular focus in Alzheimer's disease (AD) is also addressed in this special issue. In particular it has been reported and discussed by Malavolta *et al.* (INRCA, Ancona, Italy) the role played by peripheral macrophages in the clearance of senescent cells and in their contribution to fight deposits of beta-amyloid in AD: a novel concept in understanding the cause of AD that focus the attention in peripheral immune senescent cells [7]. At the same time, Casoli *et al*. (INRCA, Ancona, Italy) report that some other peripheral circulating cells, such a platelets, may be considered a key element because they represent the link between amyloid-ß (Aß) deposition, peripheral inflammation and endothelial senescence [8]. Thus, the study of peripheral cells and microglia may represent the key points to better understand the cause of neurodegeneration in AD.

Genetic aspects of cellular senescence are also considered. In particular, the role of the retrotrasposones, with a particular focus in Alu sequences, in the development of cell senescence has been reviewed in this issue by Cardelli and Marchegiani (INRCA, Ancona, Italy) [9]. Indeed, Alu sequences can promote and interfere with a wide range of mechanisms involved in genome stability including gene transcription and miRNA that display a pivotal role in the development of cell senescence [9]. Mocchegiani *et al.* (INRCA, Ancona, Italy) report the role played by oxidative stress in cellular senescence through the modulation of specific proteins, named Metallothioneins (MT), devoted to fight oxidative stress and inflammation for the whole life of an organism. As a consequence, a possible their involvement in cellular senescence is a strong clue taking into account that reduced MT expression occurs in some models of senescent cells, such as senescent endothelial cells and T-cell clones in their late passages [10].

Based on this knowledge, a concerted worldwide effort has started to develop therapeutic treatments aimed to prevent cellular senescence, to remove senescent cells and to replace senescent cells with functional ones. These targets, which are currently an unmet need in medicine, will likely constitute a promising perspective for treatment of age-related disease but more importantly to prevent disease by targeting the aging processes itself. In this context, many therapeutic approaches have been proposed in order to limit the number of senescent cells as more as possible. Gene therapies that can selectively remove senescent cells have still not developed but the encouraging results obtained with the inducible elimination of p16(Ink4a)-positive senescent cells in animal models suggest that in the next years these results will be translated into gene therapies [1]. Alternative targeting of cell senescence by genetic manipulation with telomerase was recently shown to delay physiological aging and extend longevity in old mice without increasing cancer demonstrating the feasibility of anti-aging gene therapy

[11]. The inhibition of any of SASP regulators may also lead to successful therapeutic interventions but, at the same time, it may inadvertently compromise the beneficial effect of other SASP regulators [12]. Provinciali *et al*. (INRCA, Ancona, Italy) report intriguing aspects related to a nutritional intervention, such as resveratrol, in old animals but the data are still in infancy and inconclusive and need further studies [5]. A relevant therapeutic intervention that is currently available to delay cell senescence is actually the nutritional approach, i.e. caloric restriction (CR). CR prolongs the life-spam in *Drosophila* and *C. elegans* by inhibiting mTOR pathway, which is involved in the main pathways that drive cellular senescence [13]. Moreover, CR seems to delay ageing in monkey [14]. In particular, Mocchegiani *et al*. (INRCA, Ancona, Italy) discuss the possible role of CR on the link between mTOR and MT because enhanced MT, *via* CR, may help mTOR pathway (especially TORC1 and TORC2) in blocking the proliferation of the eventual strongly damaged senescent cells that may become cancer cells [10]. All these aspects are reported and discussed in the present special issue from all the authors. As a consequence, a more complete picture can be given about the molecular and genetic mechanisms that may lead to cellular senescence. Thus, the best therapeutical approaches can be found in order to limit as more as possible the number of senescent cells and to escape, as such, the appearance of inflammatory degenerative diseases and to achieve healthy ageing and longevity. Such an ambitious goal is supported by the findings in centenarian subjects where some SAPS regulators, such as p53, is still efficient as tumour-suppressor gene despite the presence of senescent cells [2,3]. Therefore, in conclusion, cellular senescence is an intriguing aspect of the ageing process that can lead to beneficial outcomes if the therapeutic approaches are well addressed.

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