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Editorial Open Access

More than 50 Years of Cellular Senescence: From In Vitro Model to Potential Drug Target?

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Editorial

The phenomenon of cellular senescence was first discovered by Leonard Hayflick in 1961 by serially passaging human fibroblasts until they reached a state of permanent growth arrest [1]. Hayflick interpreted his finding as "aging on a cellular level" and was opposed by the most prominent researchers at that time, since the opinion that all normal human cells have an indefinite replicative lifespan in vitro still persisted–a dogma, that went back to the not reproducible chicken cell experiments by Carrel at the beginning of the 1900s. Many years later the shortening of telomeres at each cell division due to the end replication problem, was identified as a clock-like counting mechanism and the presence of critically short telomeres as the cause of replicative senescence [2]. Also various sub-cytotoxic stressors, including H2O2, Mitomycin C, ethanol and UV, were shown to induce cellular senescence, which is then referred to as "Stress-Induced Premature Senescence" (SIPS) [3].

Although the onset of cellular senescence was described to correlate with the age of the donor [4], as well as with the normal lifespan of the species from which cells were isolated [5], the relevance of cellular senescence for aging of entire organisms has still been debated heavily. Critics of this model have claimed that many cell types of the human body do not undergo enough population doublings to ever reach replicative senescence during life, thus senescence might be just an artefact of in vitro cell cultivation [6], even though SIPS is by now a well acknowledged phenomenon.

However, over the last few years more and more evidence is emerging that senescent cells accumulate in vivo in various aged tissues and that they directly contribute to age-associated pathologies. For instance, up to 25% of senescent cells were detected in the vascular system during atherosclerosis [7–9], in the liver during cirrhosis [10], and in aged skin [11,12]. Furthermore, the first causal evidence that senescent cells directly contribute to organismal aging was reported recently by Baker et al: Removal of senescent cells, both early and late in life, delayed the onset of age-associated pathologies in a progeroid mouse model [13]. However, if also animal models with a non-progeroid and thus less artificial phenotype profit from the removal of senescent cells and if these findings can also be translated to the treatment of human pathologies displaying elevated levels of senescent cells, still needs to be determined.

Cellular senescence is considered an antagonistic pleiotropy: It might have developed as a tumour-suppressive mechanism in early-life by growth-arresting cells that were either exposed to stress or underwent a high number of replication cycles, both of which increase the risk of malignant transformation. Therefore it seems to be a paradox that senescent cells contribute to the development of cancer in late-life by secreting various pro-inflammatory factors, which alter the tissue micro-environment and thus also contribute to various pathologies. Similarly, loss of regenerative potential due to stem- and progenitor cell senescence is thought to contribute to the decline of tissue function with age [14].

As already discussed, the removal of senescent cells from aging tissues might provide a potent strategy to counteract aging-associated disorders, but also the delay of cellular senescence by pharmacological or other interventions might be promising. The most obvious targets are the telomeres, which shorten with progressive replicative age and can be elongated by re-expression of the catalytic subunit of telomerase TERT, which on its own is not considered as an oncogene. The risk of inducing a higher incidence of cancer [15] can be circumvented be re-expressing TERT only in old individuals, which was shown to extend the lifespan of mice without increasing carcinogenesis [16]. Dietary restriction (DR) extends the lifespan of a wide range of organisms [17] and seems to reduce the progressive shortening of telomeres in mice [18]. However, evidence that DR also impacts on the replicative lifespan of human cells or reduces the accumulation of senescent cells in aged tissues is still lacking. In addition, the paradox that a slightly elevated BMI is protective in geriatric patients has also to be considered. Other interventions, which were already shown to promote increased replicative lifespans of human cells, include the overexpression of DNA damage repair factors [19] or the modulation of cellular levels of certain miRNAs [20].

Unfortunately, studies investigating the accumulation of senescent cells in vivo are still fragmented, especially due to technical difficulties with detecting senescent cells in various tissues. While the well-accepted senescence-associated β-Galactosidase staining requires fresh frozen samples and is thus not applicable to archival paraffinized sections [21], the recently described method of Sudan Black B staining of lipofuscin [22] is not 100% specific for senescence, since lipofuscin accumulates in all cells with age. Therefore, novel methods for the reliable and specific identification of senescent cells in vivo are still urgently required, which would allow researchers to systematically test different preventive (e.g. nutritional strategies or exercise) and even pharmacological interventions for their impact on cellular senescence. In particular, substances that specifically remove senescent cells or interfere with the senescence associated secretory phenotype might open up an extremely broad field of interventive and preventive strategies for age-associated disorders [23].

More than 50 years after Leonard Hayflick's important discovery and a lot of scepticism by fellow researchers, we now have entered the times to identify and design strategies that decrease the accumulation

of senescent cells with age for elongating human health span – and we are lucky: one of the beautiful Chinese wishes becomes truth for us: May you live in interesting times. We do.

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