What is and what is not cell senescence

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Abbreviations: ATM – ataxia-telangiectasia mutated; ATR – ataxia telangiectasia and Rad3-related; DDR – DNA damage response; DNA-PK – DNA-dependent protein kinase; DSBs – double-strand breaks; SA-β-gal – senescence-associated-β-galactosidase; SAHF – senescence-associated heterochromatin foci; SASP – senescence associated secretory phenotype; SIPS – stress-induced premature senescence; TIS – therapy-induced senescence; VSMCs – vascular smooth muscle cells

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ABSTRACT

Cell senescence is a process that occurs due to telomere erosion or can be induced by various stresses. Senescent cells cease to divide but remain alive, metabolically active and able to secrete many molecules. They also show many hallmarks of senescence, such as enlarged size, increased granularity, increased activity of SA-β-galactosidase, increased level of cyclin-dependent kinase inhibitors, p16 and p21, and DNA damage foci. Originally, cell senescence was attributed to proliferating normal cells, in contrast to cancer cells, which were considered as those endowed with indefinite growth ability. Recently, it has become evident that anticancer treatment induces senescence in cancer cells. Moreover, certain hallmarks of senescence were detected in non-proliferating post-mitotic cells. There are many signalling pathways involved in cell senescence, but the most prevalent is the DNA damage response pathway. In this review we have summarized our long lasting input in the global study of the mechanisms of senescence of normal and cancer cells and discussed the diversity of the concept of cell senescence.

INTRODUCTION

Human life expectancy (a statistical measure of the average time a human being at a given age is expected to live), has increased across the world steadily for nearly 200 years. During the nineteenth and early twentieth centuries, the increase in life expectancy was driven mainly by improvements in sanitation, housing and education, causing a steady decline in early and mid-life mortality, which was mainly due to infections. This trend continued with the development of vaccines and then antibiotics. Presently, the continuing increase is due almost entirely to a new phenomenon: the decline in late-life mortality [Oeppen & Vaupel 2002]. The number of the oldest old centenarians (people who live to or beyond the age of 100 years) is expected to increase even faster than just the elderly population and it is predicted that one-third of babies born in 2013 in the UK will live up to 100 (http://webarchive.nationalarchives.gov.uk). Centenarians are the most studied group of the old people (the program of Polish centenarians was accomplished some time ago [Mossakowska *et al.*, 2008]) due to their exceptionality in terms of long and relatively healthy life. On the other hand, ageing, considered as a decreased fertility and progressive tissue deterioration leading to increased mortality, is strictly connected with age-related diseases. Such diseases as atherosclerosis, insulin resistance, osteoporosis, osteoarthritis, neurodegeneration, cancer and many others will affect the steadily growing population of old and very old people. Thus, it is very reasonable to consider ageing and age-related diseases as disorders with common biological roots [Franceschi *et al.*, 2018]. This raises the question of why and how do we age. There are many theories trying to dissect this problem. Generally, the evolutionary theories aim to answer the question why we age and mechanistic theories cope with the problem of how we age [Sikora 2014]. One such theory falling to the category of mechanistic theories, is based on the assumption that ageing and age-related diseases are the result of cell senescence [Sikora *et al.*, 2011; Sikora 2013; Sikora *et al.*, 2014]. Indeed, recently this approach has gained very strong support. Namely, preventing cell senescence, or eliminating senescent cells by genetic manipulation or treatment of mice with so called senolitic drugs, can rejuvenate the organism. The recently just coined new term "senotherapy" refers to the process of body rejuvenation by pharmacological treatment with senolytic drugs [Childs *et al.*, 2015]. Thus, the question of what exactly is and what is not cell senescence seems to be very actual.

WHAT IS CELL SENESCENCE

The phenomenon of cell senescence was discovered by Hayflick and Moorehead who were studying human fibroblasts [Hayflick & Moorhead 1961]. Their observation was against the paradigm existing at that time, according to which both normal and cancer cells were able to grow indefinitely in culture [Bielak-Zmijewska *et al.*, 2018]. Subsequently, this paradigm was replaced by another one stating that normal cells, in contrast to cancer cells, could undergo, a so

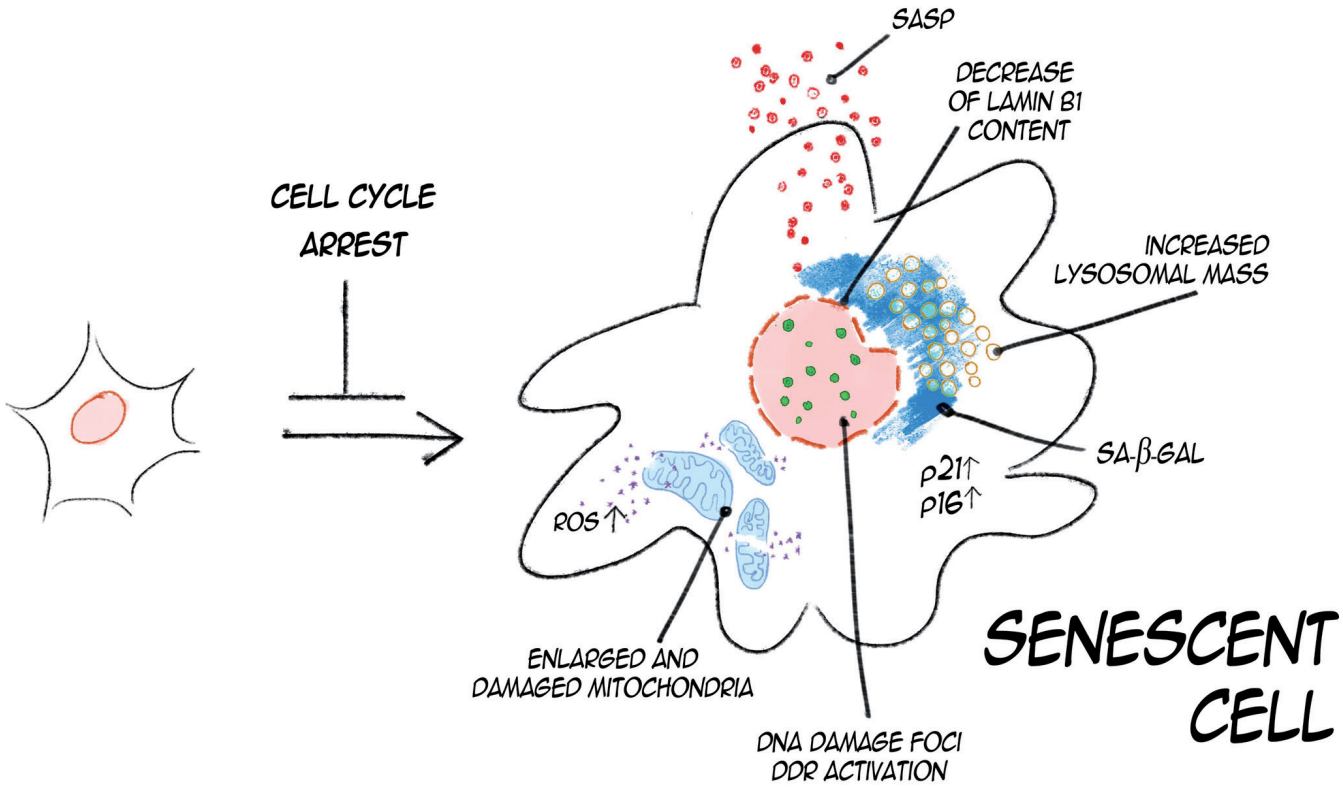

Figure 1. The main markers of cell senescence.

called, replicative senescence as they had a limited number of cell divisions. The term "Hayflick limit" was coined for the number of population doublings, which cells can achieve in the culture. For human fibroblasts it is about 50-70 divisions. Then the cells remain alive but do not divide. After the discovery of telomeres [Blackburn *et al.*, 2006] the counter of cell divisions was assigned to telomere erosion, due to a phenomenon called the "end-replication problem", which cells experience during DNA replication. Most somatic cells, do not have or have very low activity of telomerase, the enzyme which is able to elongate telomeres.

Several years ago it became obvious that cells can also undergo rapid senescence, which does not rely on telomere shortening. This phenomenon was termed stress-induced premature senescence-SIPS [Toussaint *et al.*, 2000]. Many kinds of stress can induce a quite rapid, irreversible halt of cell divisions, which in culture usually takes several days, while cells need weeks and even months to undergo replicative senescence. Interestingly, also oncogenic viruses, which finally cause neoplastic transformation, induce senescence-associated proliferation arrest, which gained the name of oncogene-induced senescence (OIS). The direct inducer of this kind of senescence is stress caused by forced DNA replication [Bartkova *et al.*, 2010]. Generally, it seems that the main culprit of cell senescence is DNA damage, especially DNA double-strand breaks (DSBs). Subsequently, the signal is transduced *via* DNA damage response (DDR), that is a cascade of signaling events, to a stable increase in the cell cycle inhibitors, p16 and p21. Senescent cells are arrested in the G1 or the G2/M phase of the cell cycle. They possess also many other hallmarks distinguishing them from proliferating non-senescent cells. These include: morphological alterations, as senescent cells are enlarged and have an irregular shape; increased granularity, large but dysfunctional mitochondria that produce high levels of reactive oxygen species (ROS); compromised nuclear integrity due to the loss of lamin B1, which also leads to the appearance of chromatin fragments in the cytoplasm; senescence-associated heterochromatin foci (SAHF); DNA damage foci detectable as phosphorylated histon H2AX (γ-H2AX) and, last but not least, increased activity of lysosomal senescence-associated-β-galactosidase (SA-β-gal) (Fig. 1). The last one, although not fully specific, since it is characteristic also for overgrown quiescent cells and macrophages, is the most commonly used marker for fast identification of senescent cells. It is of note that senescent cells are not dying but, quite the opposite, they are resistant to apoptotic cell death and fully active metabolically. They have increased secretory activity, known as senescence-associated secretory phenotype (SASP). SASP is a very important attribute of cell senescence and senescent cells secrete a lot of factors, including growth factors, metalloproteinases, chemokines and cytokines, which can induce senescence in bystander cells. Moreover, SASP, together with cells of the immune system, create a so called chronic sterile low grade inflammation state (reviewed in [Sikora 2015; Bielak-Zmijewska *et al.*, 2018]). All these features can be attributed to both replicative and stress-induced premature senescence (SIPS) *in vitro*. Interestingly, permanent irreparable DNA damage and the subsequent DNA damage response (DDR) signaling were detected in cells with short telomeres attributed to replicative senescence.

Although the majority of experiments concerning cell senescence have been performed on human fibroblasts grow-

ing *in vitro*, replicative and/or stress-induced senescence was shown to occur also in many other cells such as keratinocytes, melanocyte, epithelial cells, endothelial cells, adipocytes and mesenchymal stem cells (reviewed in [Sikora *et al.*, 2014]). Interestingly, the number of population doublings in case of replicative senescence appear to vary, depending on the cell type and cell culture conditions. For example, human peritoneal mesothelial cells were found to reach, on average, six population doublings before senescence [Ksiazek *et al.*, 2006], whereas this number for human vascular smooth muscle cells (VSMCs), thoroughly studied by us, exceeded thirty, what usually takes several months [Bielak-Zmijewska *et al.*, 2014]. Interestingly, we have shown that VSMCs undergoing replicative senescence are arrested in the G1, but those undergoing SIPS, in the G1 and G2/M phase of the cell cycle. Another difference between replicative senescence and SIPS concerns mineralization, which is typical only for replicative senescence of VSMCs [Bielak-Zmijewska *et al.*, 2014].

Some time ago it was postulated that we are ageing due to senescence of our cells [Campisi 2001]. This conclusion was made by Judith Campisi after discovering in her lab that SA- β-gal-positive cells can be found in the skin of the elderly but not in that of young people [Dimri *et al.*, 1995]. Later on, γ-H2AX foci, the markers of DNA damage, were evidenced in the skin of an old baboon [Herbig *et al.*, 2006]. From that time, using different set of markers, senescent cells were found in human, baboon and mouse skin, among human and rodent vascular endothelial and smooth muscle cells, in fat tissue, liver [Jeyapalan & Sedivy 2008], skeletal muscle of human, rodents and primates [Kreiling *et al.*, 2011] and among hematopoietic stem cells [Akunuru & Geiger 2016]. We have shown an increased number of senescent T cells (CD8+CD28-) in aged donors, including centenarians [Brzezinska *et al.*, 2004]. Interestingly, we showed that women 65+ had less senescent T cells that men of the same age [Dudkowska *et al.*, 2017]. Our very early experiments (before SA-β-gal assay implementation) indicated differences between lymphocytes derived from young and old mice in terms of AP-1 transcription factor activity [Sikora *et al.*, 1992a; Sikora *et al.*, 1992b].

There is also an experimental evidence of accumulation of senescent cells in tissues related to some pathologies, such as type 2 diabetes, atherosclerosis, hypertension, chronic pulmonary disease, cataracts and glaucoma [Naylor *et al.*, 2013], diseased kidney [Valentijn *et al.*, 2018] and liver [Sheedfar *et al.*, 2013] (Fig. 2). We identified SA-β-gal- positive cells in human atherosclerotic plaques (unpublished).

Chronic inflammation constitutes an indirect proof of senescent cell accumulation in the body with age. It was originally assigned to the process of immunesenescence and termed inflammaging [Franceschi *et al.*, 2000], but the present concept stipulates that the secretory phenotype of senescent cells can also create pro-inflammatory conditions. Moreover, inflammaging is connected with the emergence of age-related disorders, such as cardiovascular disease, neurodegeneration, type 2 diabetes and cancer [Fulop *et al.*, 2017].

However, the real challenge is to assess the number of senescent cells in a tissue. Until recently only senescent T cells,

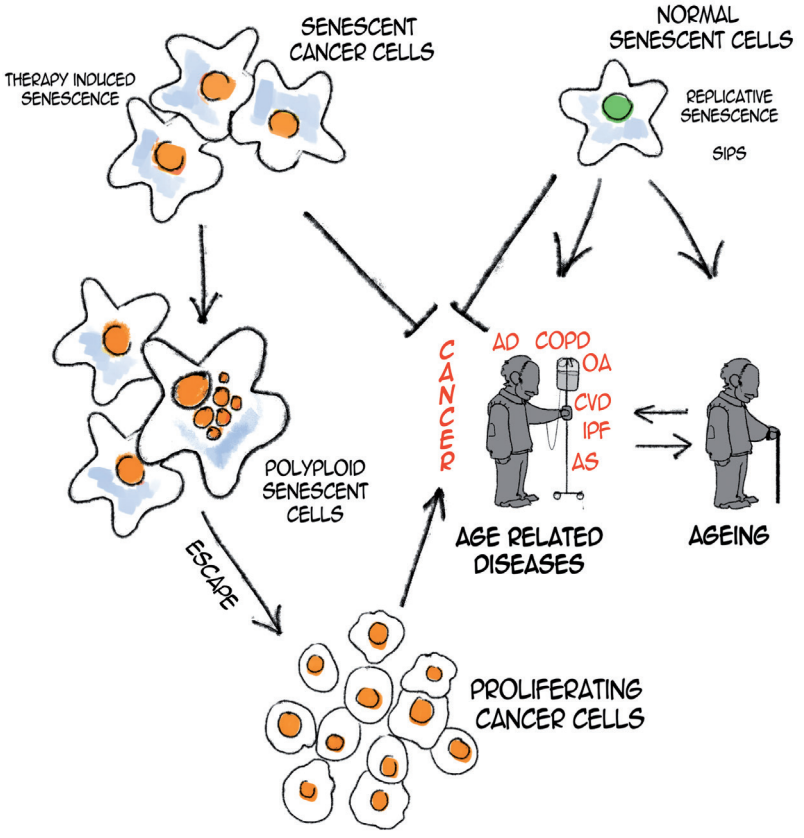

Figure 2. Scheme presenting the influence of normal and cancer senescent cells on ageing and age-related diseases: IPF – idiopathic pulmonary fibrosis, COPD – chronic obturatory pulmonary disease, OA – osteoarthritis, AD – Alzheimer disease, CVD – cardiovascular disease, AS – atherosclerosis.

which are described as CD8+CD28- subpopulation, can be easily recognized and quantified by flow cytometry analysis. We showed that their number in the population of CD8+ cells increased from 20% in young people to almost 60% in centenarians [Brzezinska *et al.,* 2004]. Recently, Krizhanovsky's group, by utilizing a technology that combines flow cytometry with high content image analysis, has been able to estimate the number of senescent cells in tissues of aged mice [Biran *et al.,* 2017]. Interestingly, the relative number of senescent cells in old mice differed depending on the cell/tissue type and reached the highest value that is about 14% in adipocytes, which is ten times more than in young animals. One can argue that the number of senescent cells in the old organism is not very high, but it should be remembered that, on one hand, these cells can be removed by the immune cells, and that, on the other hand, even small population of senescent cells can be detrimental due to the low grade inflammation state they create.

Recently, studies of genetically modified mice treated with certain senolytic drugs, have delivered very convincing direct proofs that removal of senescent cells from the body led to rejuvenation of the organism (reviewed by [Kirkland & Tchkonia 2017]).

DOES CELL SENESCENCE CONCERN CANCER CELLS?

Cell senescence is considered as a barrier to cancer development. It was shown, both *in vitro* and *in vivo*, that oncogenic viruses induced senescence in normal cells. Bypassing senescence leads to cell immortality and malignancy (reviewed in [Sikora *et al.,* 2011]). Cancer cells have mutations in genes involved in signaling pathways leading to senescence, which allows them to grow indefinitely. Paradoxically, at the beginning of this century, it became evident that anticancer treatment can induce the state of growth arrest in cancer cells together with some other hallmarks of cell senescence [Roninson *et al.,* 2001]. Using many experimental approaches, we showed that anticancer treatment of different cancer cells led to the expression of the hallmarks of senescence, such as growth arrest, altered morphology, increased granularity, increased activity of SA-β-gal, SASP and DNA damage [Dabrowska *et al.,* 2009; Sliwinska *et al.,* 2009; Mosieniak *et al.,* 2012; Mosieniak *et al.,* 2015; Sikora *et al.,* 2016; Was *et al.,* 2017; Dabrowska *et al.,* 2018].

Senescence of cancer cells very quickly became a desirable outcome of anticancer treatment (and the term therapy-induced senescence-TIS has been coined), as it is possibly less harmful to the patients because of lower doses of therapeutics needed to induce cell senescence than cell death. However, the initial enthusiasm has recently turned into a more skeptical attitude. Researchers realized that senescent cancer cells, due to the secretory phenotype (SASP), can create a favorable microenvironment for cancer development. Moreover, it appears that senescence of cancer cells can be reversible [Saleh *et al.,* 2018] and we were one of the first research groups to postulate this. Moreover, trying to answer the question about the mechanisms of this phenomenon, we have turned our attention to cancer cell polyploidization as a condition which can favor senescence escape.

Almost all human tumors display some heterogeneity and among the many histopathological features of human solid tumors is the presence of bizarre/giant cancer cells with multiple nuclei of different size (polyploidy). Cancer cells can undergo polyploidization upon treatment with both DNA damaging agents and those targeting the mitotic checkpoint. Induction of polyploidy was considered as a beneficial effect of the treatment leading to reduction of clonal growth, cancer cell death and positive response to therapy. There is however a growing body of evidence showing that polyploidization of cancer cells can lead to cancer renewal as polyploid cancer cells can give aneuploid or near diploid progeny capable of undergoing normal mitosis [Sliwinska *et al.,* 2009; Erenpreisa *et al.,* 2011]. This makes particularly interesting the question of the irreversibility of cancer cell senescence in the context of their polyploidization [Mosieniak & Sikora 2010]. Indeed, our data show that only those cancer cells, which became polyploid upon senescence-inducing treatment, can undergo atypical cell divisions and give rise to fully proliferation-competent progeny [Sliwinska *et al.,* 2009; Mosieniak *et al.,* 2015; Was *et al.,* 2017]. Our still unpublished results of experiments, performed on many cancer cell lines treated with clinically used anticancer chemotherapeutics, support this notion. It was postulated that the progeny of polyploid cancer cells, which arises as a consequence of atypical cell divisions, namely, a sort of cell budding, possesses the feature of stemness (reviewed in [Sikora *et al.,* 2016]). The occurrence of cell senescence during cancer cell treatment and its contribution to ageing of the organisms is presented in figure 2.

The cancer stem cell (CSC) concept was proposed four decades ago and states that tumor growth, analogous to the renewal of healthy tissues, is fueled by small numbers of dedicated stem cells. It has gradually become clear that many tumors harbor CSCs [Batlle & Clevers 2017], but can there be a connection between senescent and stem cancer cells? This intriguing question is still awaiting elucidation; there are however, some data already emerging indicating that polyploid cancer cells arising after treatment with anticancer drugs, can possess markers of senescence and stemness at the same time [Erenpreisa & Cragg 2013]. Currently, in cooperation with Jekaterina Erenpreisa, we are dealing with this fascinating issue.

AUTOPHAGY AND SENESCENCE

Autophagy is an evolutionarily conserved catabolic program for the degradation of subcellular elements through lysosomal proteolysis, which generally serves as a pro-survival mechanism that operates by recycling the cellular components. A characteristic morphological and functional feature of autophagy is the formation of autophagosomes, which fuse with lysosomes wherein their cargo is degraded and recycled. Autophagy is distinct from apoptosis and other cell death modes; it can, however, lead to cell demise. The question is about the connection between autophagy and senescence. In their seminal work Young *et al.,* have shown that autophagy is activated upon acute induction of senescence and contributes to the establishment of senescence [Young *et al.,* 2009]. In general, the relation between autophagy and senescence is unclear. Based on the review of literature, Gewirtz [Gewirtz 2013] points that it is difficult to judge whether these two processes

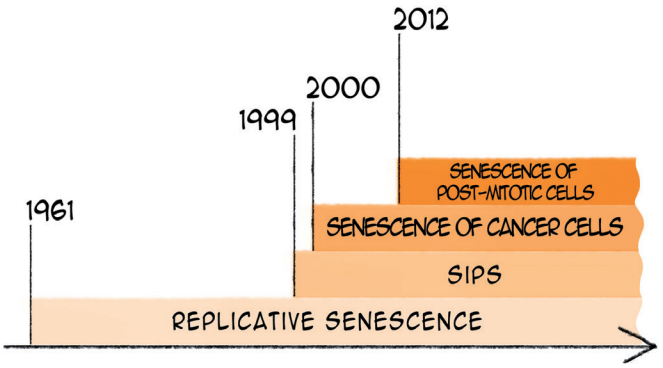

Figure 3. Progress in the understanding of the process of cell senescence in terms of the type (replicative and SIPS) and cell (normal proliferating cell, cancer cells and post-mitotic cells) context.

are dependent or occur collaterally but independently. We showed that pulse treatment of breast cancer cells with a tacrine-melatonin hybrid immediately induced autophagy, followed by autophagic flux inhibition and subsequent cell survival, with 20% of cells entering the senescence state [Kucharewicz *et al.*, 2018]. In turn, senescence of HCT116 cancer cells induced by curcumin was accompanied by autophagy; inhibition of one of the autophagic genes, *ATG5,* by RNAi, decreased the number of senescent cells [Mosieniak *et al.*, 2012]. In other studies we have shown that inhibition of autophagy by bafilomycin A1, in cancer cells induced to senesce, led to cell proliferation [Was *et al.*, 2017]. Apart from the results showing that inhibition of autophagy compromises (or at least delays) senescence, there are studies showing the reverse effect, namely, that inhibition of autophagy promotes the senescent phenotype. Thus, even if the number of data regarding this issue is constantly growing, the picture is not getting clearer, but even more complicated. In cancer cells there seems to be an interplay between polyploidy, senescence, autophagy and stemness, all of which participate in cancer cell repopulation.

DNA DAMAGE RESPONSE AND CELL SENESCENCE

Many molecular mechanisms and signaling pathways involved in cell senescence have been recognized [de Magalhaes & Passos 2018]. Their components frequently serve as markers of cell senescence. DNA damage response, induced mainly by DNA double strand breaks-DSBs, seems to be the most universal signaling pathway involved in senescence of normal and cancer cells [Bielak-Zmijewska *et al.*, 2018] and γ-H2AX, the main sensor of DSBs, is one of the most universal markers of cell senescence.

It was shown that during replicative senescence fibroblasts accumulate proteins involved in DDR at telomeric regions [d'Adda di Fagagna *et al.*, 2003]. Senescence induced by stress is not driven by the shortening of telomeres per se, but shortening of telomeres can accompany it. We have shown that replicatively, but not prematurely (i.e. undergoing SIPS), senescing human vascular smooth muscle cells have shorter telomeres [Bielak-Zmijewska *et al.*, 2014]. However, SIPS can affect the level of the shelterin proteins, which protect the structure of telomeres. We have shown that the level of the main shelterins, namely TRF1 and TRF2, decreased gradually during a seven-day culture, starting from 24h after SIPS induction [unpublished]. SIPS is initially characterized by DNA damage, which occurs randomly all over the genome and is followed by activation of DDR. As the senescent phenotype develops, most of the DNA damage at telomeric regions remains unrepaired, thus contributing to a persistent DNA damage response characteristic for cell senescence. Moreover, permanent DNA damage is indispensable for developing senescence-associated secretory phenotype-SASP [de Magalhaes & Passos 2018].

DNA damage response starts with DNA double-strand breaks which are sensed by specialized complexes that recruit and activate protein kinases from the PIKK (phosphatidylinositol 3-kinase-related kinases) family. These are: ATM (ataxia-telangiectasia mutated), ATR (ataxia telangiectasia and Rad3-related) and, possibly, DNA-PK (DNA-dependent protein kinase). Activated ATM kinase, which was recognized as the main kinase involved in DNA damage response of senescent cells, phosphorylates nibrin (NBS1) and histone H2AX, (γH2AX). Ultimately, Chk1, Chk2 (checkpoint kinase 1 and 2, respectively) and p53 are activated. p53 promotes senescence (when DNA damage is irreparable) *via* transactivation of CDKN1A gene, which encodes the cyclin dependent kinase inhibitor p21 [Kobayashi *et al.*, 2002; d'Adda di Fagagna 2008].

Our results show that both replicative senescence and SIPS induced by doxorubicin (anticancer agent) or H_2O_2 in human VSMCs were characterized by increased incidence of DSBs and DDR activation with p21 protein level increase [Bielak-Zmijewska *et al.*, 2014; Przybylska *et al.*, 2016]. Interestingly, we showed that also curcumin induced DDR-dependent senescence in cancer cells [Mosieniak *et al.*, 2016]. It was quite unexpected as our previous studies showed that curcumin was not able to cause DNA damage [Mosieniak *et al.*, 2006; Bielak-Zmijewska *et al.*, 2010; Korwek *et al.*, 2013; Grabowska *et al.*, 2015]. The explanation for this apparent discrepancy is that curcumin can induce DNA damage and DNA damage response not directly, but rather by mitotic disturbances [Mosieniak *et al.*, 2016].

It seems however, that DNA damage can evoke cell senescence even when DDR is not fully activated due to mutations in genes encoding the effector proteins that may occur in cancer and non-cancer cells. In fact, we documented this for HCT116 p53-deficient cancer cells [Mosieniak *et al.*, 2012; Strzeszewska *et al.*, 2018] and for an immortal line of lymphocytes derived from a patient with Nijmegen Breakage Syndrome (NBS) caused by mutation in the nibrin gene [Alster *et al.*, 2014]. In normal VSMCs undergoing curcumin-induced senescence we showed activation of ATM but, unexpectedly, *ATM* silencing had no effect on cell senescence [Grabowska *et al.*, 2015]. This implies that even if activated, ATM is not the crucial for transducing the signal for cell senescing. Indeed, our recent results led us to the conclusion that ATR, but not ATM kinase, is crucial for the onset of senescence in HCT 116 cells [Strzeszewska *et al.*, 2018]. However, ATR does not play important role in curcumin-induced senescence of VSMCs (submitted), which indicates cell senescence diversity.

Interestingly, it was shown that persistent activation of DNA damage response is maintained by ROS production and

that dysfunctional mitochondria are the main ROS producers [Correia-Melo *et al.,* 2016; Herranz & Gil 2016]. Dysfunction of mitochondria can be caused by upregulation of NADPH oxidase (NOX4), which induces senescence in human endothelial cells as reported by Koziel *et al.* [Koziel *et al.,* 2013]. Conversely, we have observed a decreased level of NOX4 in senescent VSMCs and shown that silencing of NOX4 can evoke senescence with the reduction of ROS level and without induction of DDR [Przybylska *et al.,* 2016]. These results show that stress evoked both by an increase or decrease of ROS can induce cell senescence, and that DNA damage is linked to ROS induction. Altogether, our results indicate that, regarding the involvement of DDR in cell senescence, different scenarios can be envisaged. Simplifying, the classical ATM-p53-p21 signaling pathway can be engaged, ATM can be replaced by ATR, p53 may be omitted, DDR does not have to be activated.

CURCUMIN AND CELL SENESCENCE

Curcumin is a polyphenol derived from *Curcuma longa*. Our interest in curcumin as a potential anticancer compound started as early as 25 years ago. Since that time we have published several papers revealing the mechanism of cell death induced by this natural compound (e.g. [Jaruga *et al.,* 1998; Piwocka *et al.,* 1999; Bielak-Zmijewska *et al.,* 2000; Piwocka *et al.,* 2001; Piwocka *et al.,* 2002; Magalska *et al.,* 2006a; Magalska *et al.,* 2006b; Mosieniak *et al.,* 2006; Wolanin *et al.,* 2006]). A plethora of reports describe curcumin as a beneficial agent having anti-inflammatory, anti-oxidant, pro-apoptotic, chemopreventive, chemotherapeutic, antiproliferative, wound healing and other properties. Animal studies have suggested that curcumin may be active against a wide range of human diseases, including diabetes, obesity, neurological and psychiatric disorders and cancer, as well as chronic illnesses affecting the eyes, lungs, liver, kidneys and gastrointestinal and cardiovascular systems (e.g. [Gupta *et al.,* 2012]). Accordingly, we have postulated that curcumin can act as an anti-ageing agent [Salvioli *et al.,* 2007; Sikora *et al.,* 2010]. Actually, some studies have shown that curcumin elongates the lifespan and healthspan of model organisms such as *Drosophila melanogaster, Cenorabdithis elegans* and even mouse [Liao *et al.,* 2011]. It seemed quite obvious to us that curcumin should protect cells against senescence or, at least, postpone it when used in concentration lower than that inducing apoptosis. It appeared not to be the case. However, we have revealed that low doses of curcumin elevated the level of sirtuins, which normally declines in senescing cells [Grabowska *et al.,* 2017]. Sirtuins possess either mono-ADP ribosyltransferase or deacetylase activity. It has been documented that sirtuins play a key role during cell response to a variety of stresses, such as oxidative or genotoxic stress, and are crucial for cell metabolism. Although some data put in question direct involvement of sirtuins in extending human lifespan, it was shown that proper lifestyle, including physical activity and diet, can influence healthspan via increasing the level of sirtuins. For this reason sirtuins are sometimes called " proteins of youth" (reviewed in [Grabowska *et al.,* 2017]).

Paradoxically, we have revealed that curcumin, in a certain range of concentrations, induced senescence by itself in both normal (VSMCs) and cancer (HCT116) cells [Mosieniak *et al.,* 2012; Grabowska *et al.,* 2015; Mosieniak *et al.,* 2016]. Curcumin possesses pleiotropic activity and may influence many signaling pathways. This is also reflected in its ability to activate different mechanisms of senescence (Grabowska *et al.*, unpublished results).

SENESCENCE OF NEURONS

The term cell senescence is generally attributed to proliferating cells as, per definition, senescence is a cessation of cell divisions. However, there are a few studies, including ours, showing increased activity of SA-β-gal in long term cultures of postmitotic neurons and in murine brains ([Piechota *et al.,* 2016] and literature there). We were interested whether also other markers of senescence are present in cultured rat cortical neurons and if the DNA damage response signaling pathway is active. It turned out that the basal level of DNA damage foci and of some key proteins of DDR increased only negligibly with time, which indicates that they could not be considered as crucial for neuronal senescence. Moreover, induction of DNA damage in neurons did not strengthen, but on the contrary, alleviated the activity of SA-β-gal.

In order to shed more light on neuronal senescence *in vitro*, we studied the level of neuronal REST, which is a protein characteristic for aging brain and is known to promote expression of anti-apoptotic and antioxidant genes [Lu *et al.,* 2014]. To our knowledge, we were the first to describe late induction of nuclear REST in neurons [Piechota *et al.,* 2016] and we think that we have identified a specific marker of neuronal senescence *in vitro*. REST upregulation occurred in neuronal cultures that also exhibited higher level of *IL-6* mRNA than early day cultures. Increase in IL-6 indicates development of a pro-inflammatory environment, which can foster pro-aging changes in cells. Primary source of IL-6 in the brain are astrocytes [Gruol 2015]. Therefore, in long-term neuronal cultures *IL-6* mRNA upregulation could result from an increasing number of astrocytes. However, neurons can also produce IL-6 under certain conditions [Tsakiri *et al.,* 2008] and it cannot be excluded that aging neurons could also contribute to the observed increase in *IL-6* mRNA. Thus, it seems that postmitotic cells such as neurons display some features of cell senescence that are typical for proliferation-competent cells. Fig.3 outlines the progress in the understanding of the process of cell senescence in terms of the type (replicative and SIPS) and cell (normal proliferating cell, cancer cells and post-mitotic cells) context.

CONCLUDING REMARKS

Recently, a great progress has been made in the field of cell senescence and not surprisingly, it has emerged that the process is much more complex than it seemed to be a few decades ago. Accordingly, based on our research, as well as data obtained by others, we postulate that it is time to update the so far prevailing **paradigms** concerning cell senescence:

- **senescence is an attribute of normal proliferating cells; in contrast, cancer cells escape senescence and become immortal**. However, cancer cells exposed to a stress inducer (anticancer treatment) become arrested in the cell cycle (due to the increased level of p21 rather than p16, as silencing of p16 gene promoter by DNA methylation is common in the majority of cancer cells),

have increased activity of SA-β-gal, activated DDR even despite p53 mutation, altered morphology and secretory phenotype. Based on these phenomena a compelling picture emerges showing that also cancer cells can undergo stress-induced premature senescence.

- **senescence is a process defined by cessation of proliferation of mitotic (dividing) cells**. Although the study of senescence of post-mitotic cells is in its infancy and the data are scarce, we showed that some markers characteristic for senescence of mitotic cells can be applied also to post-mitotic neurons both *in vivo* and *in vitro*. At this point, the usefulness of SA-β-gal (a dramatic increase in activity of which we observed in long lasting culture of neurons) as a marker of cell senescence comes into question, as the enzyme is also present in quiescent cells. In our opinion, as far as increased activity of SA-β-gal reflects altered function of lysosomes in senescent cells (this needs to be elucidated), it can be considered a candidate to mark cell senescence. We think that cell senescence may refer also to post-mitotic cells.

- **cessation of cell division is irreversible in cells which achieved the state of senescence**. Although this problem has emerged in the context of cancer cell senescence, it seems that it also refers to senescence of normal cells. Namely, some convincing data show that normal senescent fibroblasts (Walen 2008) and epithelial cells (Garbe *et al.,* 2007) can re-gain the ability to proliferate. We have shown that T cells, considered as senescent (CD8+28-) when derived from centenarians, maintain the ability to proliferate (Brzezinska *et al.,* 2004). Thus, we postulate that senescence is a permanent (but not irreversible) growth arrest, which under some circumstances can be reversed. Summing up, the process of cell senescence is not only much more complex but also more heterogeneous than it seemed to be at the dawn of the studies. The phenotype of senescent cell is dynamic, changing in time and characteristic for the particular phase of senescence as well as the cell type, stimuli and cellular context. In contrast to autophagy or apoptosis, in which specific "autophagic" or "apoptotic" genes are involved, respectively, there are no genes specific for senescence. Cell senescence has to be perceived as a consequence of interactions of specific signaling pathways (involved also in e.g. DNA damage repair, temporal cell cycle arrest, secretion) and metabolic remodeling, which altogether give a specific phenotype distinct from cell quiescence, cell differentiation or cell death. Moreover, under some circumstances cell senescence can be reversed, proving that it is not necessarily the ultimate endpoint of the cell fate.

Importantly, senescent cells accumulate in tissues during ageing. Moreover, they may be the cause of ageing and age-related diseases as their elimination results in a prolongation of health span. However, it seems that the process per se, especially the stress-induced premature senescence-SIPS, which can take place in any time of life, has nothing to do with ageing understood as getting older. Moreover, programmed senescence which takes place during embryonic development [Munoz-Espin *et al*., 2013] and cell senescence observed during wound healing in the post developmental period may be beneficial [Demaria *et al*., 2014].

We are proud that we could contribute to the development of such a fascinating field of biology, which we believe, adds even more splendor to the one hundred years of history of the Nencki Institute.

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Czym jest i czym nie jest starzenie komórki?

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Słowa kluczowe: starzenie, uszkodzenia DNA, nowotwór, telomery

STRESZCZENIE

Starzenie komórki jest procesem, który zachodzi pod wpływem skracania się telomerów lub może być indukowane stresem. Stare komórki przestają się dzielić, lecz pozostają aktywne metabolicznie i wydzielają do środowiska wiele różnych cząsteczek. Wykazują też markery starzenia, takie jak powiększone rozmiary i zwiększona ziarnistość, zwiększona aktywność β-galaktozydazy związanej ze starzeniem, podwyższony poziom inhibitorów cyklino-zależnych kinaz, p16 i p21 oraz skupiska uszkodzeń DNA. Chociaż znanych jest wiele ścieżek sygnałowych związanych ze starzeniem, to jednak najpowszechniejsza jest ścieżka indukowana uszkodzeniami DNA. Początkowo starzenie komórki uznawane było za atrybut prawidłowych komórek dzielących się, co odróżnia je od komórek nowotworowych nie mających limitu podziałów. Ostatnio udowodniono, że terapia przeciwnowotworowa indukuje starzenie komórek nowotworowych. Co więcej, występowanie pewnych markerów starzenia wykazano w niedzielących się post-mitotycznych komórkach. Artykuł ten przedstawia wkład naszego zespołu w badania procesu starzenia komórkowego oraz zwraca uwagę na różnorodność przebiegu tego procesu.