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Cellular senescence: Immunosurveillance and future immunotherapy

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ABSTRACT

In response to persistent DNA damage, induction into cell senescence promotes an immunogenic program which facilitates immune clearance of these damaged cells. Under physiological conditions, senescent cells can activate both innate and adaptive immune responses, functioning to maintain tissue homeostasis. In addition, emerging findings suggest that programmed induction of cell senescence may be important for regulating reproductive processes, partly facilitated by immune clearance. However, likely owing to ageing of the immune system, a failure to eliminate senescent cells can contribute to their persistence in tissues, leading to the development and progression of age-related diseases. Such immune failure may in part be due to activation of the senescence program in immune cells, leading to their dysfunction. Furthermore, senescent cells under certain biological contexts have been shown to instead promote immune suppression, a response that may reflect differences between an acute verses chronic senescent phenotype. In this review, we provide an overview of the research to date concerning senescence immunosurviellance, including a focused discussion on the mechanisms by which macrophages may recognise senescent cells. Senescence immunotherapy strategies as an alternative to senolytics for the removal of senescent cells will also be discussed.

1. Introduction

Clear definitions concerning the biological differences between “cell ageing” and “cell senescence” are often lacking and not well defined. To those unfamiliar with the subject of cellular senescence, such terminology can lead to confusion. We have attempted to briefly clarify such differences as follows. Cellular ageing results from stochastic processes as a result of gradual accumulating damage over time, whereas cellular senescence is a programmed change in cell state associated with permanent growth inhibition. Aged cells maintain their normal function, albeit at a decreased capacity, whereas senescent cells acquire new functions.

In cell cultures of actively proliferating cells, senescence can be abruptly induced in a matter of days. However, in many tissues and organs which consist primarily of quiescent cells (reversible growth arrest) senescence induction can only occur once cells re-enter the cell cycle. The senescent state is often mediated by a persistent DNA damage response (DDR) (Burton and Faragher, 2015; d’Adda di Fagagna, 2008), induced by stress induced stimuli such as telomere dysfunction, oncogene activation, oxidative stress, cell–cell fusion and chemotherapeutic drugs (Chuprin et al., 2013; Di Micco et al., 2006; Ewald et al., 2010; Toussaint et al., 2002; Victorelli and Passos, 2017). “Induction” of senescence therefor refers to the programmed responses which occur following a DDR triggered by a stress induced stimuli. In addition to permanent growth arrest, the senescent state is accompanied by several additional phenotypic changes which make them distinct from their non-senescent counterparts (Table 1). Although a senescence-like response has been reported in post-mitotic cells such as neurons (Jurk et al., 2012), this review will focus on cell senescence in growth-competent cells.

Probably the most widely researched aspect of the senescent phenotype to date is the altered secretory response, referred to as the senescence-messaging secretome, senescence-associated secretory phenotype or the senescence-associated secretome (Campisi and d’Adda di Fagagna, 2007; Kuilman and Peeper, 2009; Malaquin et al., 2016). Here we refer to this response simply as the “senescent secretome”. The senescent program is often accompanied with transcriptional changes linked to an altered secretome, consisting of pro-inflammatory cytokines, growth factors and proteases which appear to mimic inflammatory wound repair processes (Coppé et al., 2008; Shelton et al., 1999). In fact, senescent cells have been shown to be important in wound healing, tissue plasticity and tissue regeneration (Demaria et al., 2014; Mosteiro et al., 2016; Ritschka et al., 2017), suggesting that such a secretome is likely physiologically important for such processes. However, to date, the senescent secretome has more often been considered from a pathological perspective, with emphasis being placed on the damaging effects of chronic inflammation in age-related diseases and cancer. In recent years there has been a surge of review articles

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Table 1
Phenotypic changes often associated with cell senescence in vitro.

Senescent Phenotype	Reference
altered secretome	reviewed in (Malaquin et al., 2016)
mitochondria dysfunction	reviewed in (Ziegler et al., 2015)
increased glycolysis	(James et al., 2015)
altered lipid metabolism	reviewed in (Ademowo et al., 2017)
enlarged morphology	(Chen et al., 2000)
chromatin remodelling	(Adams, 2007)
expression of NKG2D ligands	(Sagiv et al., 2016)
extracellular vesicle secretion	(Takahashi et al., 2017; Kavanagh et al., 2017)
increased lysosomal mass	(Lee et al., 2006)
pro-survival response	reviewed in (Burton and Faragher, 2015)
Elevated ROS	reviewed in (Passos & Von Zglinicki, 2006)

focused on the role of cell senescence in ageing and disease, a subject beyond the scope of this review (Burton and Krizhanovsky, 2014; Childs et al., 2015; Muñoz-Espín and Serrano, 2014; van Deursen, 2014).

With the understanding that senescent cells can be beneficial in the short term, a process that appears to be regulated by immune processes, the concept of the senescent secretome as pathological can be reframed to instead reflect its immunogenic properties, in other words, a secretome that modulates an immune response. Whether a senescent cell is beneficial or detrimental likely depends on how long senescent cells persist within tissues.

Whilst senescent cells secrete factors known to function in the activation, migration, adhesion and differentiation of immune cells in other systems, much more research is needed to investigate the impact of the senescent secretome on specific immune cell functions. Some studies have reported a correlation between the presence of secretory factors associated with cell senescence and immune cell infiltration/localisation within tissues (Kang et al., 2011; Krizhanovsky et al., 2008; Xue et al., 2007). An overview of factors associated with an immunogenic senescent secretome and their response within different immune cell types has been reviewed previously (Sagiv and Krizhanovsky, 2013).

2. The senescent program: mechanisms initiating an immune response

In the majority of instances, induction of the senescence program is initiated by activation of a DDR (Burton and Faragher, 2015; d'Adda di Fagagna, 2008). Such a DDR is known to function in the activation of innate immunity and in the development and function of adaptive immunity (Nakad and Schumacher, 2016; Xu, 2006). A DDR during induction of cell senescence appears to be important for inducing an altered secretome capable of attracting and activating immune cells. As later discussed, a DDR has also been shown to be important for upregulating the expression of NKG2D ligands found on senescent cells, enabling their recognition by immune cells (Sagiv et al., 2016).

DNA damage can occur within chromatin packed nuclear DNA leading to activation of transcription factors and other regulators of cell secretion. These include, but are not limited to p38MAPK, NFkB, HMGB1, BRD4, mTOR and GATA4 (Chien et al., 2011; Davalos et al., 2013; Freund et al., 2011; Herranz et al., 2015; Kang et al., 2015; Tasdemir et al., 2016). In addition to nuclear DNA, increased damage to the nucleotide pool has also been shown to induce cell senescence (Rai et al., 2009) and may also involve activation of an immune response. Interestingly, it also appears that DNA damage during induction of cell senescence leads to accumulation of damaged DNA in cytoplasmic foci which promotes a senescent secretome. Studies have shown that activation of cyclic GMP-AMP synthase (cGAS), a cytosolic DNA sensor, in senescent cells triggers stimulator of interferon genes (STING) which play an important role in innate immunity (Dou et al., 2017; Glück et al., 2017; Ng et al., 2018; Yang et al., 2017). Mackenzie et al. investigated the mechanisms by which cellular DNA gains access to the cytoplasm since it is normally compartmentalised within the nucleus to prevent autoimmunity (Mackenzie et al., 2017). It was reported that cGAS localises to micronuclei arising from genomic instability and that breakdown of the micronuclei envelope exposes self-DNA to the cytosol.

Mechanisms other than a DDR cannot be ruled out. For example, treatment of tumour cells with cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors were shown to not only induce cell cycle arrest but to also promote anti-tumour immunity (Goel et al., 2017). CDK4/6 inhibition activated the expression of endogenous retroviral elements which stimulated the production of type III interferons leading to enhanced tumour antigen presentation. Rather than activating a DDR, CDK4/6 inhibitors in the context of tumour biology may enhance the susceptibility of such cells to immune checkpoint blockades. However, it should be noted that whilst such cells underwent cell cycle arrest, it does not mean that such cells are senescent and instead may have undergone a state of quiescence (Yoshida and Diehl, 2015).

From a therapeutic perspective, a more in depth understanding of the initial molecular mechanisms involved in activating an immune response is required. Such knowledge may one day be utilised to therapeutically enhance immune clearance of senescent cells as a strategy to alleviate and prevent age-related diseases.

3. Senescent cells activate an innate immune response

Scientific research focused on immune surveillance of senescent cells is an emerging field. It has now been approximately ten years since the first evidence for such a response was reported. In that study, Xue et al. demonstrated that reactivation of p53 in p53-deficient tumours promoted induction of a cellular senescence program (Xue et al., 2007). This was associated with activation of an innate immune system as evident by increased expression of transcripts specific to natural killer (NK) cells, macrophages and neutrophils. This immune activation consequently resulted in tumour clearance, suggesting that the senescence program functions to prevent cancer development. It also suggested that induction of cell senescence rather than cell death may prove a more effective strategy for targeting cancers.

The following year, Krizhanovsky et al. reported another benefit of immune clearance of senescent cells: the resolution of liver fibrosis following damage (Krizhanovsky et al., 2008). Immune cells such as NK cells, macrophages and neutrophils were found to be in proximity to senescent cells in fibrotic livers. In addition, senescent activated stellate cells generated during liver damage were shown to be preferentially killed by NK cells both in vitro and in vivo. In doing so, immune clearance of senescent cells prevented excess fibrosis which occurred when cells were unable to enter the senescent state. Other than possibly acting as an anti-cancer mechanism, senescent cells until this point were frequently considered as only detrimental to the tissue in which they reside. However, it is now apparent that senescent cells could also play beneficial roles and that this is likely dependent upon the biological context. Following on from these findings, a role for cell senescence in other fibrotic models were also reported (Fitzner et al., 2012). In addition, physiological functions for senescent cells such as during wound healing, regeneration, embryonic/placental development and skeletal bone regulation during late puberty, slowly began to emerge (Chuprin et al., 2013; Demaria et al., 2014; Li et al., 2017; Muñoz-Espín et al., 2013; Storer et al., 2013; Yun et al., 2015). However, the possibility that the aforementioned studies are instead reporting non-senescent cells displaying biomarkers in common with senescent cells cannot be ruled out.

Sagiv et al. later investigated the mechanisms promoting NK mediated killing of senescent cells. Granule exocytosis, but not death-receptor-mediated apoptosis, was shown to be required for NK cell-mediated killing of senescent cells (Sagiv et al., 2013). Mice with defects in granule exocytosis accumulated senescent stellate cells within