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Cellular senescence and the aging brain

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ABSTRACT

Cellular senescence is a potent anti-cancer mechanism that arrests the proliferation of mitotically competent cells to prevent malignant transformation. Senescent cells accumulate with age in a variety of human and mouse tissues where they express a complex 'senescence-associated secretory phenotype' (SASP). The SASP includes many pro-inflammatory cytokines, chemokines, growth factors and proteases that have the potential to cause or exacerbate age-related pathology, both degenerative and hyperplastic. While cellular senescence in peripheral tissues has recently been linked to a number of age-related pathologies, its involvement in brain aging is just beginning to be explored. Recent data generated by several laboratories suggest that both aging and age-related neurodegenerative diseases are accompanied by an increase in SASP-expressing senescent cells of non-neuronal origin in the brain. Moreover, this increase correlates with neurodegeneration. Senescent cells in the brain could therefore constitute novel therapeutic targets for treating age-related neuropathologies.

1. Introduction

The development of therapies aimed at mitigating or delaying age-related neurodegenerative diseases is a major priority for the biomedical community due to the enormous social, emotional and economic burden associated with them. The disappointing outcomes of dozens of phase III clinical trials of treatments for Alzheimer's disease (AD) and Parkinson's disease (PD) indicate a need for fresh approaches to identify novel targets that drive processes that cause age-related neuropathology.

A new view has recently emerged suggesting that aging itself may not merely be a major risk factor for these disorders, but may actually be the underlying driving force. This view begs the question as to whether interventions that prevent the occurrence of basic aging processes can prevent or alleviate age-related conditions, including neurodegenerative diseases. One such mechanism currently under investigation by several laboratories is a process known as cellular senescence.

2. Cellular senescence and the SASP

Cellular senescence is a potent anti-cancer mechanism that can occur in virtually all cell types that are capable of cell division. Thus far, replication-competent cell types that undergo senescence include fibroblasts, epithelial cells, melanocytes, endothelial cells, astrocytes (Bitto et al., 2010; Coppe et al., 2010, 2008; Voghel et al., 2007; Wajapeyee et al., 2008). The senescence response arrests cell proliferation, stably and essentially irreversibly, in response to stresses that puts cells at risk for malignant transformation (Campisi, 2001; Collado and Serrano, 2010; Prieri et al., 2008). These stresses include repeated cell division that erodes telomeres (perceived by cells as severely damaged DNA), DNA damage anywhere in the genome, and disrupted chromatin (epigenomic damage) (Campisi, 2007; Guney et al., 2006; Rodier et al., 2005; Shay and Wright, 2005). Cellular senescence can also be induced by activated oncogenes, strong or persistent mitogenic signals, and several forms of oxidative stress (Adams, 2009; Ben-Porath and Weinberg, 2005; Braig and Schmitt, 2006; Campisi and d'Adda di Fagagna, 2007; Herbig and Sedivy, 2006; Ohtani et al., 2004; Passos and Von Zglinicki, 2006; Toussaint et al., 2000). Many senescence inducers directly or indirectly cause genomic or epigenomic damage. The damage response ultimately activates the p53/p21 and $p16^{INK4a}$/pRB tumor suppressor pathways, which establish and maintain the senescence growth arrest (Adams, 2009; Campisi and d'Adda di Fagagna, 2007; Herbig and Sedivy, 2006; Ohtani et al., 2004).

Cellular senescence may be an example of evolutionary antagonistic pleiotropy (Campisi, 2003). This evolutionary theory posits that, because the force of natural selection declines with age, processes that were selected to promote fitness in young organisms can have unselected deleterious effects in older organisms (Rose, 1991). Hence, the senescence response protects organisms from cancer early in life; late life in life, however, it may promote phenotypes and pathologies associated with aging. Senescent cells have indeed been demonstrated to accumulate with age in a variety of tissues (Dimri et al., 1995; Erusalimsky and

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Kurz, 2005; Herbig and Sedivy, 2006; Jeyapalan et al., 2007; Kishi, 2004; Melk et al., 2003; Paradis et al., 2001). A seminal publication recently demonstrated that the elimination of senescent cells that accumulate in a progeroid mouse model prevents the onset of three major aging phenotypes (cataracts, sarcopenia, loss of subcutaneous fat), providing the first evidence that senescent cells play a causal role in at least some age-related pathologies in vivo (Baker et al., 2011).

In addition to arresting growth, senescent cells express a senescence-associated secretory phenotype (SASP): the robust secretion of many inflammatory cytokines, growth factors and proteases (Coppe et al., 2010, 2008). SASP factors include several interleukins (ILs), monocyte chemotactic proteins (MCPs; aka CCLs), growth-related oncogenes (GROs; aka CXCLs), and inflammatory cytokines such as granulocyte–macrophage colony stimulating factor (GM-CSF) and macrophage inflammatory proteins (MIPs; aka CCLs), among others (Coppe et al., 2010; Davalos et al., 2010; Freund et al., 2010). SASP factors can have potent effects on neighboring cells and thus can alter local and systemic tissue milieus.

There are potentially beneficial effects of the SASP. For example, chemokines or cytokines secreted by senescent cells can recruit natural killer cells, thus facilitating the removal of senescent cells and neighboring tumor cells; this process is termed 'senescence surveillance'. Other SASP factors can communicate cellular damage to the surrounding tissue and stimulate repair or limit damage-induced fibrosis (Krizhanovsky et al., 2008). However, many SASP factors have been shown, or are suspected, to cause or contribute to the loss of tissue structure and function that occurs with age by creating a pro-inflammatory milieu. For example, the SASP has been shown to: (1) disrupt normal tissue structure and function — e.g., the ability of mammary epithelial cells to form alveoli and ducts and express milk proteins (Parrinello et al., 2005; Tsai et al., 2005); (2) induce epithelial-to-mesenchyme transitions in normal and premalignant epithelial cells (Coppe et al., 2008, 2011); and (3) stimulate premalignant and non-aggressive cancer cells to migrate and invade a basement membrane (Coppe et al., 2010; Rodier et al., 2009). In some cases, the use of blocking antibodies and recombinant proteins allowed assignment of these activities to one or a few SASP factors. In vivo, senescent cells can promote the conversion of premalignant cells to full blown malignancy (Krtolica et al., 2001) and stimulate the growth and vascularization of tumors initiated from established tumor cell lines (Coppe et al., 2010; Krtolica et al., 2001).

Most SASP factors are up-regulated at the level of mRNA, in part due to increased activities of nuclear factor kappa light chain enhancer of activated B cells (NF-kB) and CCAAT/enhancer binding protein (C/EBP) transcription factors (Coppe et al., 2008; Freund et al., 2010). The SASP is dependent on the activation of specific signaling pathways, including the DNA damage response (DDR), p38 mitogen-activated protein kinase (p38MAPK), and mechanistic target of rapamycin (mTOR) pathways (Coppe et al., 2008; Freund et al., 2011).

3. The aging brain

The brain is arguably the most multifaceted tissue in complex organisms, controlling processes that are vital not only to life but also at the heart of cognition and personality. Loss of brain function, whether through trauma or – much more commonly – aging, exacts an enormous human and economic toll, especially among people in developed nations where average life spans are at record highs (Vaupel, 2010; Yankner et al., 2008). As with virtually all aging tissues in the body, the aging brain is characterized by low level, chronic inflammation (Chung et al., 2009; Franceschi et al., 2007). This phenomenon has been termed 'inflammaging' (or 'neuro-inflammaging' in the brain) (Frank-Cannon et al., 2009). Inflammaging is thought to cause or contribute to most, if not all, major pathologies associated with aging. Inflammation evolved to remove foreign bodies, pathogens and damaged cells produced by acute cellular stress or injury (Ferrucci et al., 2005). The acute inflammatory response causes robust local oxidative and nitrosative damage, but is designed to be short-acting and self-limiting. Chronic inflammation, by contrast, is a more feeble response, but is long-standing and often self-perpetuating (Nathan and Ding, 2010). Inflammaging is considered 'sterile' inflammation because it occurs in the absence of an obvious pathogen or foreign body.

In the aging brain, pathological changes associated with chronic inflammation include significant decreases in certain neuronal populations, dendritic and axonal arborization, post-synaptic densities, dendritic spines, presynaptic markers, synapse and cortical volume (Yankner et al., 2008). These cellular and tissue changes result in cognitive and motor impairment, memory loss and other phenotypes characteristic of aged mammals. The etiology of neuro-inflammaging is a crucial unresolved question. An important source of neuroinflammation in the aging brain is the proliferative glial cells (astrocytes, oligodendrocytes and microglia). These cells normally provide structural, metabolic and trophic support to neurons (Allen and Barres, 2009; Chung et al., 2009; Lucin and Wyss-Coray, 2009; McGeer and McGeer, 1998; Ransom et al., 2003). However, they can also have detrimental effects on neighboring neurons due to the chronic production of pro-inflammatory factors, including reactive oxygen species (ROS) and leukocyte-attracting cytokines, which occurs with increasing frequency during aging.

4. Brain cell senescence

A potential contributor to age-related inflammation in the brain is cellular senescence, likely occurring in replication-competent glial cells. Recent studies from several laboratories suggest that senescent cells are detectable in the mammalian brain, where they could contribute to neurodegenerative processes by secreting pro-inflammatory SASP factors and/or disrupting cell–cell contacts needed for the structural and functional neuron–glial interaction that maintains neuronal ion and metabolic homeostasis (Benarroch, 2005; Magistretti, 2006). Senescent cells and their SASPs may therefore constitute a novel, understudied, and potentially important contributor to neuroinflammation and subsequent neurodegeneration. Characterization of cellular senescence in the brain could uncover novel therapeutic targets for the prevention and treatment of chronic age-related neurodegenerative diseases.

4.1. Evidence for cellular senescence in proliferation-competent brain cell types

Astrocytes are involved in a variety of important physiological and pathological processes, including modulation of synaptic neuronal function and plasticity (Finch, 1993; Nichols et al., 1993). They are the most abundant cell type in the brain and the primary responders to central nervous system (CNS) insults, including infection, trauma and neurodegeneration, in response to which they exert important tissue defense mechanisms. Dysfunctional astrocytes are implicated in neuropathology associated with both normal brain aging and various age-related neurodegenerative diseases (Chen and Swanson, 2003). In response to exogenously added H_2O_2, cultured astrocytes have been reported to display numerous characteristics of senescent cells: arrested growth, an enlarged morphology, increased senescence-associated beta-galactosidase (SA-Bgal) activity, and increased expression of the senescent cell markers p21 and $p16^{INK4a}$ (Bitto et al., 2010). Cultured human astrocytes exposed to DNA-damaging ionizing irradiation (IR) also undergo senescence and develop a SASP, similar to the behavior of cultured human fibroblasts (Zou et al., 2012). Astrocytes cultured from the brains of aging rats stain positively for SA-Bgal, in conjunction with a reduced ability to maintain the survival of co-cultured neurons (Pertusa et al., 2007). In vivo, astrocytes, as determined by glial acidic fibrillary protein (GFAP)-positivity, demonstrated a flat morphology, a characteristic of senescent cells, as well as age-related synaptic impairment (Nichols et al., 1993). These findings suggest that loss of neuroprotection during brain aging coincides with increased astrocytic senescence.

Microglia, another important replication-competent cell type in the brain, function as resident macrophages in the CNS (Streit, 2002a,b). Microglia provide immune surveillance and mediate innate immune responses to invading pathogens or injury. These responses include the secretion of cytokines, prostaglandins and growth factors, production of external ROS and stimulation of phagocytosis (Doorn et al., 2012). Microglia are normally found in a quiescent (resting) state, characterized by small soma and highly ramified processes. In response to infection or CNS injury, microglia become activated and undergo morphological changes, including shortening of ramified branches and enlargement of the soma. Activated microglia also up-regulate cell surface activation antigens and secrete a variety of pro-inflammatory mediators and other potentially neurotoxic factors (Kreutzberg, 1996). Chronic microglial activation has been implicated in the neuronal death associated with neurodegenerative diseases, including AD and PD (Frank-Cannon et al., 2009; Sugama, 2009).

There is strong evidence to suggest that, with advanced age, functional abnormalities occur in the microglia that impair their ability to respond efficiently to stimuli (Conde and Streit, 2006; Sawada et al., 2008). A comparative study examining both young and old autopsied human brains demonstrated that, with age, microglia transform morphologically from ramified to hypertrophic and dystrophic forms, characterized by loss of fine branches (deramification), formation of cytoplasmic spheroids, beading and fragmentation (Flanary, 2005; Streit et al., 2004).

It has been reported that telomere shortening occurs in rat microglia, both in culture with repeated cell division and in vivo with advancing age. In both cases, this telomere shortening can lead to cellular senescence (Flanary and Streit, 2003, 2004). In response to repeated lipopolysaccharide administration, cultured microglial cells also undergo a senescence response as determined by arrested growth, enhanced SA-βgal activity, and senescence-associated heterochromatic foci (Yu et al., 2012). Both normal brain aging and chronic age-related neurodegenerative disease are associated with microglial-mediated increases in components that are associated with the SASP, including increases in pro-inflammatory cytokines such as IL-1β and IL-6 (Bachstetter et al., 2011).

Other proliferative cell types in the brain that could conceivably undergo senescence include oligodendrocytes, endothelial cells and neural stem cells (NSCs). The senescence of these cell types could have both intrinsic and extrinsic effects on neuronal function. The senescence of oligodendrocytes, for example, could reduce myelination of neuronal axons, thereby decreasing their interneuronal signaling ability. The senescence of endothelial cells could contribute to the age-related disruption of the blood–brain barrier (BBB), resulting in and influx of peripheral inflammatory factors that can contribute to subsequent

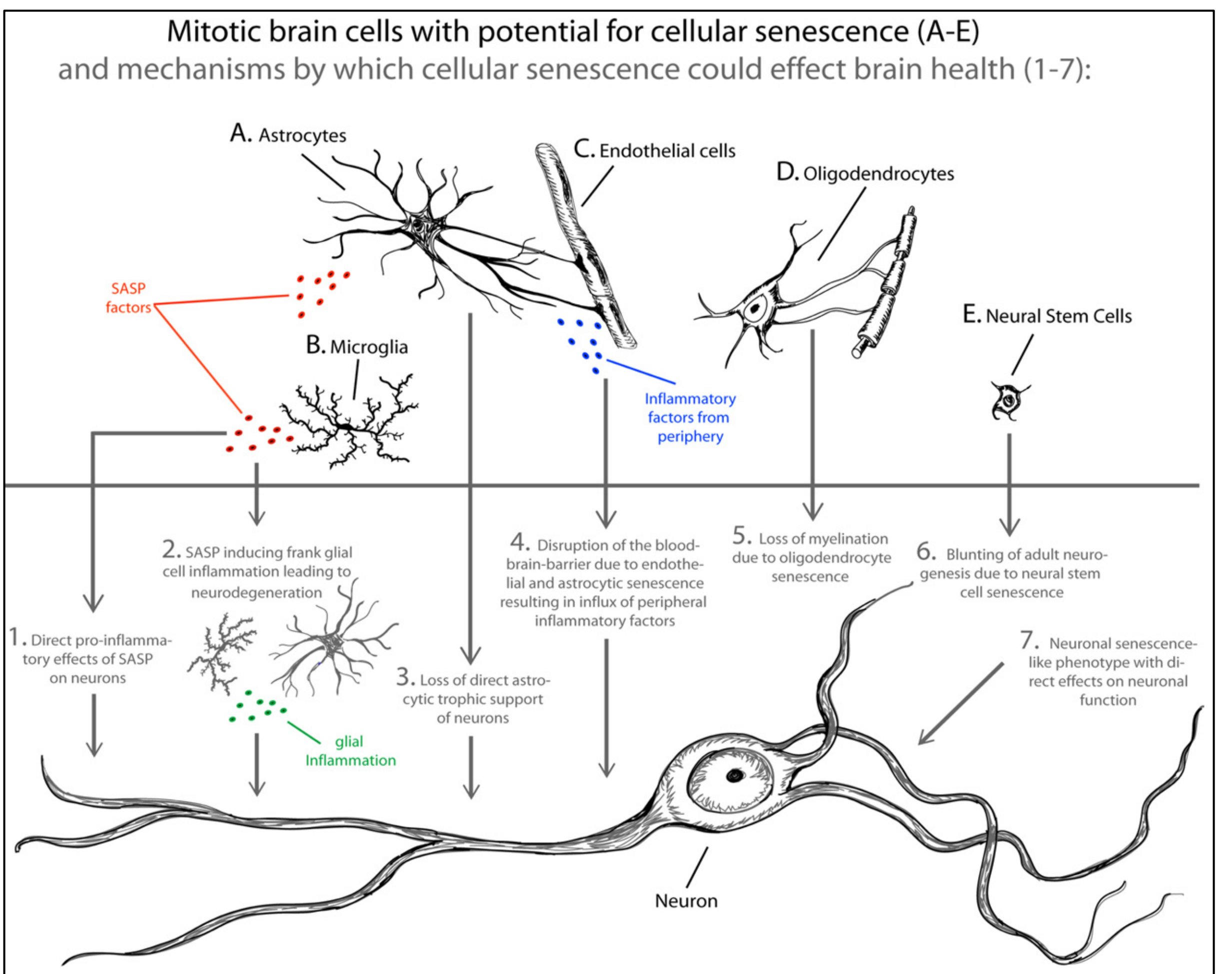

Fig. 1. Senescence within non-neuronal cells in the brain include (A) astrocytes and (B) mciroglia which can release neurotoxic SASP factors that can both impact directly on neighboring neurons and elicit activation of the other cell type, resulting in frank inflammation. Astrocytic senescence may also result in loss of important trophic support for neurons. Senescence within C) endothelial cells may act to compromise the blood–brain-barrier, potentially allowing peripheral immune cells to enter the brain. Senescence of (D) oligodendrocytes may reduce myelination of neurons and thus their signaling capacity. Neural stem cells (NSCs) undergoing senescence can result in inhibition of neurogenesis. Although as a non-proliferating cell types, neurons would not be predicted to undergo senescence, its occurrence would result in direct effects on this cell type.

neuronal cell loss (Zlokovic, 2008). The BBB deterioration that occurs during aging has also been linked to age-related cognitive decline (Abazov et al., 2009). Finally, the senescence of NSCs could blunt adult neurogenesis. Exposure of cultured NSCs to ionizing radiation was recently reported to result in senescence without a SASP in the small fraction of the population that failed to die by apoptosis, and p16-positive NSCs have been identified in the aging brain (Molofsky et al., 2006; Zou et al., 2012). Neurons are terminally differentiated and would not be predicted to mount a 'classic' senescent response, although a recent study reported senescence markers in non-dividing neurons in the aging mouse brain (Jurk et al., 2012). Given the mounting evidence that senescent cells, largely through the SASP, can disrupt tissue structure and function, cellular senescence may be an important factor to consider in age-related neurodegeneration, including which cell types are involved and how (Fig. 1).

4.2. Brain cell senescence in human aging and neurodegenerative diseases

Senescent markers were recently reported in astrocytes in autopsied human brain tissue; both $p16^{INK4a}$ and the SASP factor matrix metalloproteinase (MMP) 3 increased significantly with age and were even higher in affected cortical brain tissues from AD patients relative to age-matched controls (Bhat et al., 2012). Our laboratory similarly found an increased burden of senescent astrocytes in autopsied substantia nigra pars compacta (SNpc) from PD patients compared to age-matched controls based on elevated $p16^{INK4a}$ levels (unpublished data). Likewise, we found an increase in DNA damage (γH2AX) foci in astrocytes in PD SN; these foci are characteristic of senescent cells and are required for the SASP that develops in response to genomic stress (Rodier et al., 2011). This finding suggests that at least astrocytes, the major cell division-competent cell type in the brain, undergo senescence in vivo in humans and are more prominent in both neurodegenerative disease and aging.

5. Future issues to be addressed

Several important biological questions remain to be addressed with regard to cellular senescence in the brain. Do other proliferative cell types undergo senescence in the context of aging and age-related neurodegenerative diseases? What stressors are responsible for eliciting brain cell senescence and the SASP? How do the SASPs compare between various brain cells and other cell types, including fibroblasts, the cell type most commonly used for exploring this phenomenon? Most importantly, does brain cell senescence contribute to neurodegeneration? If yes, is the neurodegeneration due to direct effects of the SASP on neighboring neurons or is it due to activation of glial cells, resulting in the amplification of neuroinflammatory processes?

6. Conclusion

Senescent cells accumulate with age in a variety of human and mouse tissues and their elimination was recently demonstrated to prevent certain age-related pathologies in peripheral tissues in a progeroid mouse model (Baker et al., 2011). Recent studies from various laboratories suggest that senescent cells are also present in the aging brain and in conjunction with age-related neurodegenerative diseases. Neurodegeneration associated with these conditions is closely tied to neuroinflammation. A potential source of this neuroinflammation is the pro-inflammatory SASP from senescent brain cells. Although there are still many unanswered questions involving brain cell senescence, the ability to critically test the idea that senescent cells can cause or contribute to age-related neuropathology will allow the identification of an important and novel target (senescent cells) for pharmacological interventions aimed at amelioration of age-related neurodegeneration.

Conflict of interest

The authors have no conflicts of interest.

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