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Environmental stress, ageing and glial cell senescence: a novel mechanistic link to Parkinson's disease?

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Abstract

Exposure to environmental toxins is associated with a variety of age-related diseases including cancer and neurodegeneration. For example, in Parkinson's disease (PD), chronic environmental exposure to certain toxins has been linked to the age-related development of neuropathology. Neuronal damage is believed to involve the induction of neuroinflammatory events as a consequence of glial cell activation. Cellular senescence is a potent anti-cancer mechanism that occurs in a number of proliferative cell types and causes the arrest of proliferation of cells at risk of malignant transformation following exposure to potentially oncogenic stimuli. With age, senescent cells accumulate and express a senescence-associated secretory phenotype (SASP; i.e. the robust secretion of many inflammatory cytokines, growth factors and proteases). Whereas cell senescence in peripheral tissues has been causally linked to a number of age-related pathologies, little is known about the induction of cellular senescence and the SASP in the brain. Based on recently reported findings, we propose that environmental stressors associated with PD may act in part by eliciting senescence and the SASP within non-neuronal glial cells in the ageing brain, thus contributing to the characteristic decline in neuronal integrity that occurs in this disorder.

Introduction

Ageing is a major risk factor for many pathological conditions including cancer, diabetes, heart disease, stroke and neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease (PD) [1]. The incidence of these conditions, which are major causes of death in both industrialized and developing countries, has risen markedly in the last century, largely due to the increase in life-expectancy as well as urbanization. In addition to changes in lifestyle, urbanization is associated with environmental degradation. Indeed, exposure to environmental toxins has been identified as a substantial causal risk factor for the majority of these age-dependent diseases. It is clear that understanding the pathophysiological mechanisms that link environmental toxin exposure to these diseases is crucial in order to develop more effective strategies to prevent or reduce the prevelance of age-related disorders.

One of the most prominent neurodegenerative diseases in which environmental exposure to chemicals plays a significant role is PD. This is the second most common neurodegenerative disease in the USA, affecting more than 1 million individuals. The main pathological characteristic of PD is the preferential loss of dopamine-producing nigrostriatal neurons in a

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particular region of the brain, the substantia nigra, resulting in marked impairment of motor control. Another pathological feature of PD is the presence of cytoplasmic protein aggregates, known as Lewy bodies, in dopaminergic nerve cells. Lewy bodies contain a variety of proteins, including ubiquitin and alpha-synuclein [2]. The precise aetiology of PD has been under investigation for more than two centuries. Although rare genetically linked cases of PD have been reported, most incidences are sporadic in nature. Late-onset, idiopathic PD is thought to result from the combined effects of genetic risk factors, ageing and environmental exposure to toxins. Two neurotoxic environmental compounds known to induce PD are the widely used herbicide paraquat and the synthetic heroin analogue 1-methyl-4-phenyl-1, 2,3,6-tetrahydropyridine (MPTP). It is widely believed that chronic exposure to these or analogous compounds constitutes important an environmental risk factor for the future development of PD [3].

Here, we review the potential role of ageing and chronic stress in the process of cellular senescence, which can occur within non-neuronal glial cells in the brain and may in turn have detrimental consequences for neighbouring cells, including neurons. We propose that PD-associated environmental stressors contribute to this process, thereby providing a novel link between environmental exposure to chemicals, glial cell senescence and age-related neurodegenerative events associated with PD.

The ageing brain

The brain is possibly the most multifaceted tissue within complex organisms, controlling processes that are not only vital to life but also crucial for cognition and personality. Loss of brain function, whether through trauma or, much more commonly, ageing, is a huge human and economic burden, especially in developed nations where average life spans are continuously increasing [4, 5].

The brain comprises approximately 2% of the total body weight and, because it consumes about 20% of the total oxygen utilized at rest, is highly prone to oxidative stress. Consequently, the brain generates an abundance of reactive oxygen species (ROS) as normal products of cellular metabolism [6]. It also contains relatively higher amounts of polyunsaturated fatty acids and lower levels of antioxidants than many other tissues, making it further susceptible to oxidative stress. ROS such as superoxide, hydroxyl radicals, hydrogen peroxide and singlet oxygen, produced during normal aerobic metabolism, cause chronic damage to biomolecules which ultimately results in a decline in brain function and contributes to brain ageing [7].

Like most ageing tissues in the body, the ageing brain is characterized by low-level chronic inflammation [8, 9]. This phenomenon has been termed ‘inflammaging’ (‘neuro-inflammaging’ in the brain). Inflammaging is thought to cause or contribute to most, if not all, of the major pathological conditions that are associated with ageing, including neurodegenerative diseases such as PD. An important source of inflammation in the ageing brain is the proliferative glial cells (i.e. astrocytes, oligodendrocytes and microglia). These cells normally provide structural, metabolic and trophic support to neurons [8, 10, 11]. However, they can also have detrimental effects on neighbouring neurons due to chronic production of pro-inflammatory agents, including ROS and leukocyte-attracting cytokines, which occurs with increasing frequency during ageing. One potential cause of age-related inflammation in the brain is cellular senescence (i.e. a tumour suppressive stress response) within the glial cells.

Cellular senescence

Cellular senescence is essentially irreversible loss of proliferative capacity that occurs when cells are exposed to potentially oncogenic stimuli [12]. Similar to apoptosis, this potent tumour suppressive response inhibits tumorigenesis; in this case by preventing the proliferation of cells at risk of malignant transformation. Senescence growth arrest depends on two major tumour suppressor pathways controlled by p53 and p16INK4a [12, 13].

Cellular senescence was first described following the observation that primary cells in culture ceased dividing after a finite number of doublings [14]; this is now known as the Hayflick limit. In subsequent studies it was determined that the cause of this limit of division was an erosion of telomeres, the DNA–protein structures that cap the ends of chromosomes [15, 16]. As a result of the biochemistry of DNA replication, telomeres shorten with each cell division, eventually failing to form a protective cap and resulting in a structure that resembles a DNA double-strand break [17–21]. The effort by cells to ‘repair’ uncapped telomeres causes cycles of chromosome fusion and breakage, resulting in chromosomal aberrations that, in turn, can lead to cancer [22]. Stem cells and cancer cells express the enzyme telomerase, which allows them to replace telomeres after cell division. However, most differentiated somatic cells do not express telomerase. Such cells become senescent; that is upon acquiring a critically short telomere, growth is permanently arrested.

In addition to telomere shortening, other types of severe DNA damage can cause cells to become senescent [20, 21]. Many DNA-damaging chemotherapies as well as radiotherapy can, for example, induce senescence [23, 24]. In addition, strong mitogenic signals such as those induced by activated oncogenes can cause the senescence response [12, 25, 26]. Melanocytic nevi provide a clear example of oncogene-induced senescence. These generally benign lesions are composed primarily of senescent melanocytes that harbour an oncogenic mutation in the *BRAF* gene, which encodes a growth factor signalling protein [27]. Cellular senescence can also be induced by agents or events that disrupt chromatin organization [28–30]. Furthermore, oxidative stress can induce cellular senescence, principally by activating the p53 pathway [24, 31, 32]. Various forms of oxidative stress can induce senescence, including exposure to ROS and hyperoxia [26, 31, 33] (Figure 1). We and others recently demonstrated that a genetically induced tissue-specific deficiency in the mitochondrial antioxidant enzyme superoxide dismutase induces cellular senescence and ageing phenotypes in the epidermis of mice [27, 34].

Immunosurveillance mechanisms have evolved to clear senescent cells *in vivo* [28, 29, 35, 36]. Nonetheless, senescent cells accumulate with age [37–42]. The relative contribution of the numerous inducers of senescence to the age-dependent accumulation of senescent cells is unknown. Telomere shortening is the explanation most often reported, but it is not clear whether this is in fact more common than other forms of stress that lead to senescence.

A striking characteristic of senescent cells is the robust expression and secretion of numerous cytokines, chemokines, growth factors and proteases; this feature is termed the senescence-associated secretory phenotype (SASP). Most SASP factors are upregulated at the level of mRNA [24], in part due to increased transcriptional activities of nuclear factor kappa light chain enhancer of activated B cells (NF-kB) and CCAAT/enhancer binding protein (C/EBP) [43–47]. The SASP is a delayed response, primarily to genotoxic stress [20, 21], and depends on the activation of the DNA damage response and p38 mitogen-activated protein kinase (p38MAPK) pathways [45, 46]. An important positive feedback component for the development of the SASP in fibroblasts is increased expression of the plasma membrane-bound form of the cytokine interleukin (IL)-1α, which induces its own synthesis

through an autocrine, receptor-mediated positive feedback loop involving activation of NF-kB [47].

There are both beneficial and detrimental effects of the SASP. Certain SASP factors can reinforce the senescence growth arrest in an autocrine manner. These factors include the cytokines IL-6 and IL-8, the protease inhibitor plasminogen activator inhibitor-1 and the pleiotropic protein insulin-like growth factor binding protein-7 [43, 44, 48, 49]. The SASP also has beneficial paracrine effects. For example, chemokines or cytokines secreted by senescent cells can recruit natural killer cells, thus facilitating the removal of senescent cells and neighbouring tumour cells [50, 51]; this process is termed 'senescence surveillance' [36]. Other SASP factors communicate cellular damage to the surrounding tissue and stimulate repair or limit damage-induced fibrosis [50, 52].

On the other hand, when senescent cells are chronically present, such as during ageing, the SASP can cause ageing phenotypes and pathology. For example, it has been shown that SASP factors disrupt normal mammary tissue structure and function and can even induce malignant phenotypes in pre-malignant or non-aggressive cancer cells *in vivo* via inflammation and vascularization [24 53–56]. SASP factors such as GROα, IL-6 and WNTs can enhance the proliferation of neoplastic epithelial cells [53, 57, 58], or promote epithelial–mesenchymal transition [54], which is a critical step in the development of metastatic cancer [59]. SASP factors can promote malignant phenotypes in culture [55, 57] and tumour growth *in vivo* [53, 60]. Hence, in contrast to its tumour suppressive action, senescence, through the SASP, can also support malignant tumorigenesis.

Evidence for cellular senescence in the ageing brain

To date, the mechanisms underlying cellular senescence in the brain as well as how senescent non-neuronal cells may affect brain function and pathology remain unclear. Neurons are terminally differentiated cells and do not mount a classic senescence response. However there is evidence that astrocytes, the most predominant proliferative cell type in the mammalian brain, undergo cellular senescence. Astrocytes are involved in a variety of important physiological and pathological processes [52, 61], including modulation of synaptic neuronal function and plasticity [62–64]. They are also the primary responders to CNS insults, including infection, trauma and neurodegeneration, by exerting important tissue defence mechanisms. Dysfunctional astrocytes are implicated in neuropathology associated with both normal brain ageing and various age-related neurodegenerative diseases, including PD [65].

Astrocytes cultured from the brains of ageing rats were found to stain positive for the senescence marker senescence-associated beta-galactosidase (SA-Bgal) in conjunction with a reduced ability to maintain the survival of co-cultured neurons. *In vivo*, astrocytic glial acidic fibrillary protein (GFAP)-positive cells demonstrated a flat morphology, which is another characteristic of senescent cells, as well as age-related synaptic impairment [66]. These findings suggest that loss of neuroprotection during brain ageing coincides with increased astrocytic senescence [67].

Another important type of glial cells, microglia, function as resident macrophages in the CNS [68]. 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 [69]. 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 upregulate cell

surface activation antigens and secrete a variety of pro-inflammatory mediators and other potentially neurotoxic factors [70]. Chronic microglial activation has been implicated in the neuronal death associated with neurodegenerative diseases such as Alzheimer's disease and PD [71, 72]. 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 [73, 74]. 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 [75, 76]. It has been reported that telomere shortening occurs in rat microglia, both in culture and *in vivo*, with advancing age, which can lead to senescence [77, 78].

Environmental stress and glial senescence

Is it possible that prolonged environmental stress in the context of the ageing brain could promote glial cell senescence and contribute to age-related neuropathology? Does exposure to agents associated with ageing or neurodegenerative disease result in the senescence of astrocytes or microglia? In a recent study [79] in human and mouse astrocyte cultures it was found that astrocytes undergo cellular senescence in response to a variety of stressors. Exposure to an oxidant (H_20_2) or proteasome inhibitor, or replicative exhaustion all led to the development of characteristics of senescence, including growth arrest, an enlarged flattened morphology, SA-Bgal expression, increased expression of the cell cycle inhibitors p21 and p16INK4a, and the development of senescence-associated heterochromatin foci (SAHF). It is interesting that astrocytes were found to be much more susceptible to oxidative stress-induced senescence than fibroblasts. Oxidative stress in cultured human astrocytes caused by glutathione depletion activated SASP-associated inflammatory pathways (NF-kB and p38MAPK) and stimulated secretion of the SASP-associated cytokine IL-6 [80]. In another recent study it was found that, in response to repeated lipopolysaccharide administration (mimicking chronic inflammation), cultured BV2 microglial cells displayed several signs of senescence, including growth arrest, enhanced SA-Bgal activity and SAHF [81]. Epidemiological studies and data from animal models have shown that exposure to pesticides and other environmental toxins, including paraquat and MPTP, causes PD neuropathology in part via the chronic overstimulation of glial cells and accumulation of ROS and inflammatory factors (particularly cytokines) [82–84]. Together, these data suggest that environmental exposure to toxins is capable of inducing senescence and an accompanying SASP, which could contribute to neurodegeneration associated with both normal brain ageing and neurodegenerative disease.

Future perspectives

Based on current understanding of the underlying mechanisms involved, we hypothesize that there may be an inherent link between cellular senescence in the brain and the environmental stressors associated with PD. Paraquat and MPTP are environmental neurotoxins that can have direct neurodegenerative effects on nigrostriatal neurons via inhibition of mitochondrial function and oxidative stress. We propose that these and related environmental stressors may indirectly contribute to neurodegeneration via the induction of glial cell senescence. Evidence supporting a glial SASP, although at present limited, suggests that senescent glia could contribute to age-related neurodegeneration by creating a chronically inflamed milieu. If correct, this novel potential link between glial senescence and PD could change the understanding of how glial cells contribute to age-related neurodegenerative diseases, and in particular the role of environmental exposure in this process.

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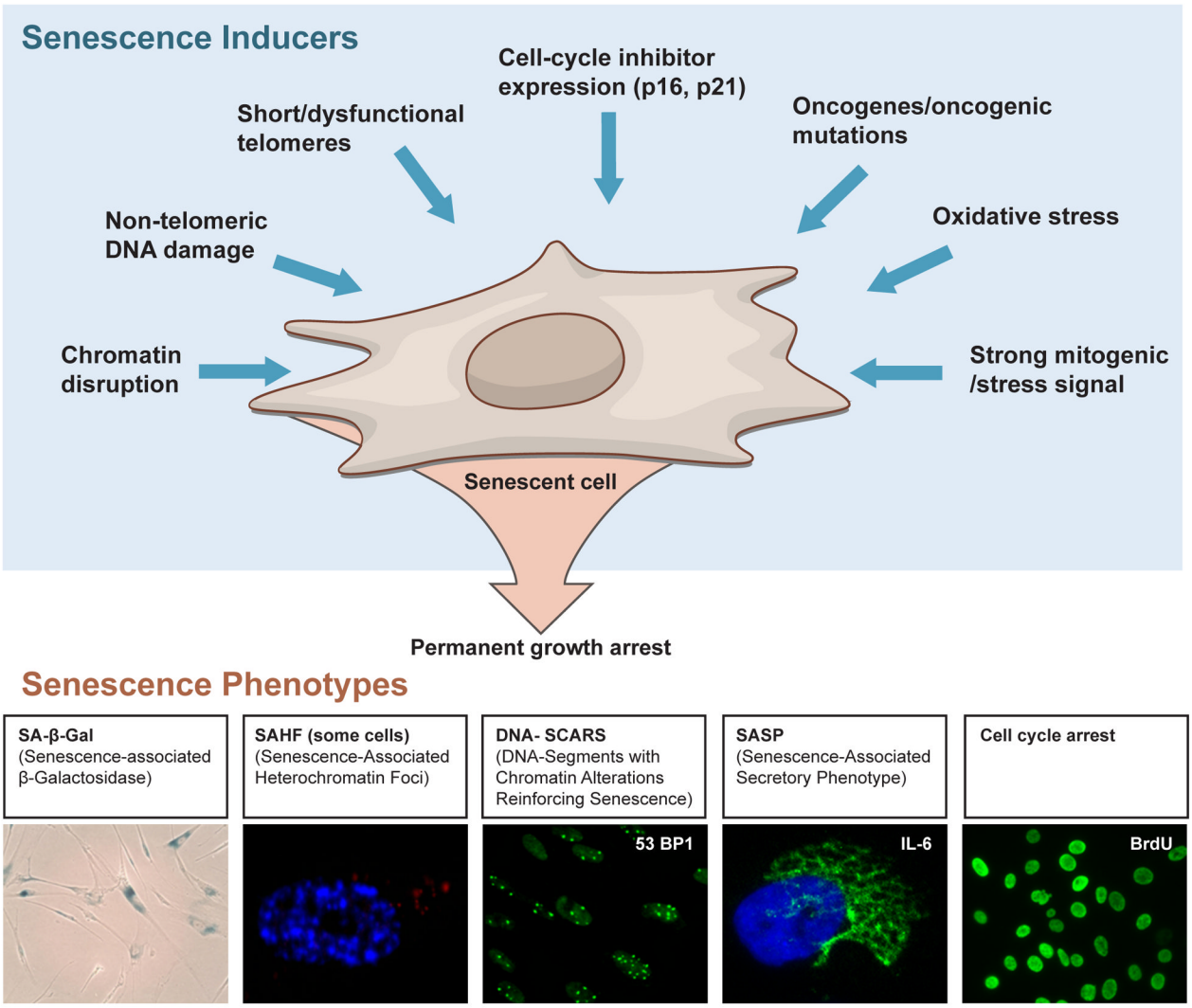

Fig. 1.

Induction and detection of cellular senescence. Multiple stressors induce cellular senescence in cell culture and *in vivo*. The over-expression of cell-cycle inhibitors, such as p16 and p21, irreversibly blocks cell proliferation. Activation of oncogenes and telomeric dysfunction eventually cause DNA damage and cell-cycle arrest. Oxidative stress and other stress signals, such as mitochondrial dysfunction, can induce cellular senescence through various mechanisms such as via induction of p53 or DNA damage. Senescent cells acquire a specific phenotype characterized by increased cell size, expression of the lysosomal enzyme B-galactosidase, loss of proliferation, formation of permanent DNA damage foci (DNA segments with chromatin alterations reinforcing senescence or SCARS), chromatin remodelling (SAHF) and induction of a secretory phenotype (SASP).

Table 1

Glial cellular senescence in the brain

Astrocytes	**Microglia**
Increased SA-Bgal expression	Increased SA-Bgal expression
Flat morphology	Growth arrest
Increase in p21 and p16INK4a	Telomere shortening
Development of SAHF	Development of SAHF
Increased SASP-associated inflammatory pathways (NF-kB and p38MAPK)	Increase in inflammatory factors
Increased cytokine expression (e.g. IL-6)	