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EDITORIAL

Astrocyte senescence contributes to cognitive decline

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Aging is the main risk factor for the most pervasive diseases of developed countries including age-related cognitive decline and neurodegeneration, which afflict a continuously growing number of individuals worldwide (Franceschi et al. 2018). Aging can be broadly attributed to the life-long accumulation of mutations caused by environmental stressors that lead to a progressive loss of fitness in a species. Environmental factors such as genotoxic stressors and radiation as well as the cell's own metabolic production of reactive oxygen species (ROS) can lead to a time-dependent accumulation of DNA damage (Niccoli and Partridge 2012). As the loss of genomic fidelity burden increases, cellular defense systems monitor and repair any damage and, when damage is beyond repair, enter a proliferative arrested state termed replicative senescence. Recent evidence has shown that accumulating senescent cells in tissues and organs are a major driver of the aging process and age-related disease in mammals (Childs et al. 2015). Selective removal of senescent cells in genetically engineered animals has been demonstrated to reverse or delay aspects of aging (Perrott et al. 2017; Ogrodnik et al. 2019). Senescent cells are metabolically active, but their function has been altered in comparison to their non-senescent counterparts. A major feature exhibited by senescent cells is expression of the senescence-associated secretory phenotype (SASP) (Watanabe et al. 2017). Mediators secreted from senescence cells can act in a paracrine manner on neighboring cells to induce senescence-like phenotypic and functional changes and thereby contribute to organ dysfunction and pathogenesis of age-related diseases, driving organismal aging. The accumulation of cellular stress also provokes adaptive and plastic transcriptional responses, which are partly orchestrated by alternative splicing (Mastrangelo et al. 2012). Alternative splicing is a critical mechanism for expanding regulatory and functional diversity from a limited number of genes, and is particularly complex in the mammalian brain (Lin et al. 2016). Alternative splicing is mediated by the competitive binding of a series of splicing activators and inhibitors

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to splicing enhancer and silencer sequences around the splice sites to determine the likelihood for each splice site to be used (Fu and Ares Jr. 2014; Smith and Valcarcel 2000).

It is estimated that 50% of the human brain mass is composed of astrocytes, which play a fundamental role in multiple aspects involved in the maintenance of brain cerebrovascular health (Jakel and Dimou 2017). Recent evidence has suggested that the accumulation of senescent astrocytes may drive neurodegenerative disorders (Di Malta et al. 2012) and recent work shows that clearance of senescent glial cells may help with by preventing the accumulation of Tau aggregates and prevent cognitive decline in mouse models (Bussian et al. 2018; Baker and Petersen 2018). Pre-clinical studies have shown that pharmacological impairment of astrocytic function recapitulates cognitive deficits that are observed in old age (Tarantini et al. 2017a). It is also noteworthy that irradiation-induced accumulation of senescent cells is associated with neurovascular dysfunction in animal models (Ungvari et al. 2017). Astrocyte senescence has also been recently implicated in the pathogenesis of Alzheimer's disease (Bhat et al. 2012; Garwood et al. 2017) and Parkinson's disease (Chinta et al. 2018). Yet, the role played by alternative splicing on the astrocytic senescence phenotype, and its involvement in the progression of age-related neurodegenerative diseases, has remained elusive.

It is appealing to conjecture that DNA damage–induced dysregulation in alternative splicing mechanisms in senescence would play a pivotal role in the process leading to the senescence-associated phenotype of astrocytes and the consequent loss of cognitive function. In support of this, recent evidence has shown that human aging is characterized by focused changes in gene expression and deregulation of alternative splicing (Harries et al. 2011) and that age-related associations between splicing factor expression and cellular senescence are present in in vitro models (Holly et al. 2013), human aging (Lee et al. 2019), and in long-lived mice (Lee et al. 2016). Emerging evidence suggests moderation of splicing factor levels is associated with reversal of cellular senescence in human primary fibroblasts (Latorre et al. 2017). Recent studies have demonstrated dysregulation of splicing mechanisms in Alzheimer's disease (Wong 2013) and that global dysregulation of splicing is characteristic of several neurodegenerative conditions such as Huntington's disease (Lin et al. 2016), frontotemporal lobar dementia (Gao et al. 2017), and Parkinson's disease (Soreq et al. 2012). Though these existent findings would predict that differential expression of splicing regulatory factors would contribute in the development of the DNA damage–induced senescent phenotype in astrocytes, no formal study has been performed to investigate altered patterns of alternative splicing in vitro in senescent astrocytes. Additionally, the relationship between some of these isoform changes detected in peripheral blood in human populations and cognitive phenotypes has not been previously described.

In an elegant paper recently published in *Geroscience*, Lye et al.[28] identify a novel role for splicing factor expression dysfunction in the regulation of cellular senescence in astrocytes associated to the development of cognitive impairment in participants from the InCHIANTI (Ferrucci et al. 2000) population study of aging. The authors first characterized the composition of the astrocyte SASP in terms of cytokine and MMP production. Senescent astrocytes demonstrated altered levels of several key SASP proteins such as elevated IL-8, GM-CSF, angiogenin, ENA78, GRO-α, MMP-3, MMP-10, and TIMP2 levels and reduced IL-10 levels (Lye et al. 2019). In their results, senescent astrocytes also displayed changes in splicing factor expression and patterns of alternative splicing. Half of the splicing factor tested in their pre-selected panel demonstrated lower expression in senescent astrocytes compared with non-senescent cells. They found dysregulation in the HNRNP splicing inhibitors and Serine-arginine (SR)–rich splicing activator transcripts; also, 50% of splicing factor transcripts measured in their panel exhibit altered expression in senescent astrocytes. Circulating level of senescence markers such as P16INK4a and functional status in humans are correlated as it is demonstrated in recent studies (Lawrence et al. 2018). To investigate the relationship between astrocyte senescence-associated transcripts and cognitive decline in a clinically relevant approach, the authors compared senescence-related transcript changes in aged primary human astrocytes with cognitive decline as assessed by changes in MMSE score between the 3rd and 4th subsequent follow-up, and in peripheral blood mRNA from individuals in the InCHIANTI study of aging. They discovered a transcriptional signature of 7 genes which associated with senescence in late passage astrocytes, as well as expressed in peripheral blood: TAU3, GFAP(A), KLOTHO(M) CDKN2A($p14^{ARF}$), CDKN2A($p16^{INK4A}$), CDKN1A(p21b), and PSEN2.

CDKN2A ($p14^{ARF}$) and TAU3 were positively associated with mild cognitive decline, whereas GFAPα was negatively associated with mild cognitive decline. Interestingly, the only association the authors found with severe cognitive decline was a negative association with TAU3. This study identifies a novel role for splicing factor expression dysfunction in the regulation of cellular senescence in astrocytes. Among the investigated candidate genes, 7 newly recognized isoforms show splicing alterations in senescent cells and concomitant expression in human peripheral blood, allowing for the discovery that TAU3, GFAPα, and CDKN2A (p14ARF) show correlation with mild cognitive decline in aging humans. These newly obtained findings suggest that age-related splicing factor changes may lead to splicing patterns for genes with roles in brain function or senescence, which may play a role in the development of cognitive decline in the human population. Astrocytes also play a key role in the regulation of cerebral blood flow by mediating neurovascular coupling responses and maintaining overall brain health. Neurovascular coupling is the term used to describe alterations in local perfusion that occur in response to changes in neuronal activity. During elevated brain activity, increased neuronal firing is sensed at the tri-partite synapse by astrocytic end-feet terminals which elicit a Ca^{2+} signal that travels to the end-feet enveloping the cerebral arterioles, leading to release of lipid mediators (epoxyeicosatrienoic acids [EETs] and prostaglandins), and ATP, which produce local vasodilation (Tarantini et al. 2017b; Iadecola and Nedergaard 2007). Astrogliosis, or the adoption of a stressed phenotype, is commonly observed in aged brains. Moreover, recent studies have suggested that ~ 15% of astrocytes undergo cellular senescence (Clarke et al. 2018) in aged neurodegenerative disease states, implicating astrocytic senescence in the pathogenesis of Alzheimer's disease (Bhat et al. 2012; Garwood et al. 2017) and Parkinson's disease (Chinta et al. 2018). It is plausible to speculate that impaired mediation of neurovascular coupling responses due to the age-related increase in senescent astrocyte burden in the brain would result in impaired production of astrocyte-derived vasoactive mediators, resulting in impaired cognitive function and vascular dementia–related pathologies. Many more aspects of central nervous system physiology are mediated by astrocytes. Some of the central roles in which astrocytes are involved include ion balance, metabolism, pH regulation, neurotransmitter homeostasis, neurogenesis, synaptic plasticity, operation of lymphatic system, glycogen synthesis and storage, regulation of energy balance, and chemosensing (Verkhratsky and Nedergaard 2018; Verkhratsky et al. 2019a, b). It is then clear that astrocytic functional integrity is absolutely essential for brain homeostasis and overall health. In addition to the several functions performed by astrocytes control over blood-brain barrier (BBB) integrity is of particular importance for brain health and maintenance of cognitive function. The BBB is largely comprised of endothelial cells (ECs), pericytes, and astrocytes which together form an essential regulatory barrier between the neural interface and the brain vasculature. Healthy astrocytes provide essential secreted factors that lead to the adequate association between the cells of the BBB and the formation of strong tight junctions (Cabezas et al. 2014). In age-related neurological pathophysiological disorders, such as Alzheimer and Parkinson's diseases, a disruption of the BBB takes place, involving an increase in barrier permeability and phenotypical changes in both the ECs and astrocytes (Haseloff et al. 2005; Daneman 2012). Astrocyte senescence can therefore be hypothesized as an important age-related contributor to the decrease in barrier function which may result in neuroinflammation and decreased cognitive integrity and pathology observed in aging. The existing evidence presented suggests that future studies should continue to explore the functional consequences of astrocyte senescence and its relationship to declining cognitive function in aging with particular emphasis on the role of senescent astrocytes in the impairment of neurovascular coupling responses and the increase in blood–brain barrier permeability. It will still be also of great interest to determine whether similar transcriptional changes observed by Lye et al. (Lye et al. 2019) may also be occurring in other important proliferative brain cell types in the neurovascular unit such as endothelial cells. In conclusion, this work by Lye and coworkers provides an exciting step toward understanding how astrocyte senescence contributes to cognitive decline. Beyond the new questions that are raised, these data, combined with the potential new role of alterative splicing in association with cellular senescence and cognitive impairment, provide compelling evidence of the importance of DNA damage–induced processes in the age-related loss of cognitive integrity. A deeper understanding of mechanisms associated with cellular senescence in aging may provide exciting new opportunities for the development of therapies to prevent cognitive impairment in the elderly.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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