Review

Genome instability: Linking ageing and brain degeneration

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ABSTRACT

Ageing is a multifactorial process affected by cumulative physiological changes resulting from stochastic processes combined with genetic factors, which together alter metabolic homeostasis. Genetic variation in maintenance of genome stability is emerging as an important determinant of ageing pace. Genome instability is also closely associated with a broad spectrum of conditions involving brain degeneration. Similarities and differences can be found between ageing-associated decline of brain functionality and the detrimental effect of genome instability on brain functionality and development. This review discusses these similarities and differences and highlights cell classes whose role in these processes might have been underestimated—glia and microglia.

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1. Ageing: a multifactorial process

Ageing has been defined as the "progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death" (Lopez-Otin et al., 2013). Ageing affects most body systems as well as perceptual and cognitive functions (Kennedy et al., 2014), and therefore has a profound impact on quality of life, health and well-being, with broad social and economic implications (Fang et al., 2015; Hurd et al., 2013). While medical advances are reducing the functional limitations in the elderly, ageing remains the strongest risk factor for the major chronic illnesses—cardiovascular diseases, cancer and diabetes—as well as cognitive decline (Lopez-Otin et al., 2013; Newgard and Sharpless, 2013).

Various biological and molecular hallmarks of ageing have recently been defined (Burkle et al., 2015; Lopez-Otin et al., 2013), and some of them are reflected in the many theories that have been proposed to explain the biology of ageing (Ahlqvist et al., 2015; Bolt and Bergman, 2015; Feltes et al., 2015; Goldsmith, 2012; Jenny, 2012; Jones, 2015; Sergiev et al., 2015; Xi et al., 2013). Arguably the most comprehensive theory of ageing, the disposable soma theory, posits that the soma needs to be maintained to facilitate reproduction upon which the soma can decay and age as the offspring continues to carry the genetic information (Drenos and Kirkwood, 2005). As selective pressure vanishes upon passage of the genetic information to ensuing generations, ageing is considered to be in itself a nonadaptive process (Vijg and Kennedy, 2015). Intriguingly,

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the nonadaptive nature of ageing gives more weight to individual genetic differences, environment, life events and health behavior in determining its form and pace and thus opens up perspectives for interventions for healthy ageing.

Ageing is a multifactorial process affected by cumulative physiological changes resulting from stochastic processes and genetic changes that together alter metabolic homeostasis. The stochastic component entails accumulation of damage to various cellular macromolecules, particularly the DNA. The pace of these processes differs considerably among people, resulting in the great variation in timing of ageing and onset of age-related diseases. Thus, individual differences in maintenance of genome stability are emerging as an important factor affecting the ageing process and variation in ageing between individuals (Cho and Suh, 2014; Lopez-Otin et al., 2013; Maynard et al., 2015a; Vijg, 2014; Vijg and Suh, 2013). Additional genetic factors affecting ageing pace regulate cellular metabolism. A prime example is genetic alterations affecting the insulin-like growth factor receptor (IGF-1R) pathway (Puglielli, 2008): reduced activity of IGF-1R-mediated signaling results in stress-resistant prolongation of life expectancy in worms (Kenyon, 2011; Kenyon et al., 1993), flies (Giannakou and Partridge, 2007), and mice (Russell and Kahn, 2007), and correlates with increased longevity in humans (Flachsbart et al., 2009). Another example is the conserved deacetylases, sirtuins, which regulate various metabolic circuits relevant to ageing, such as genome stability, inflammatory responses, programmed cell death, and mitochondrial functions (Watroba and Szukiewicz, 2015). Alterations in sirtuin activity have been implicated specifically in ageing of the brain (Duan, 2013). Another important player in cellular ageing is mitochondrial homeostasis, which is critical for various biosynthetic pathways, cellular energetics (Wallace et al., 2010), cellular redox homeostasis and signaling (Leloup et al., 2011), calcium buffering (Contreras et al., 2010), and regulation of programmed cell death (Borutaite) (Finkel, 2015; Grimm et al., 2015).

Disruptions of endoplasmic reticulum (ER) homeostasis due to energy or nutrient depletion or disturbances of calcium or redox balance lead to the misfolding of proteins, ER stress, and up-regulation of several signaling pathways collectively designated 'unfolded protein response' (UPR). The UPR includes activation of chaperones, degradation of misfolded proteins, and attenuation of protein translation (Harding et al., 2002; Schroder and Kaufman, 2005). The UPR plays a fundamental role in the maintenance of cellular homeostasis and thus is central to normal physiology (Walter and Ron, 2011). However, sustained unresolved ER stress leads to apoptosis (Hussain and Ramaiah, 2007; Naidoo et al., 2008). It was found that ageing is associated with decline in expression and activity of key ER-associated chaperones and decline of the UPR. One of the mechanisms that has been associated with the decline in cellular functions in ageing is progressive failure of chaperoning systems (Brown et al., 2012). These are the systems by which the ER suppresses protein aggregation by accurately ensuring transcription and translation, chaperoning nascent or unfolded proteins and shepherding improperly folded proteins through a degradation pathway before they can aggregate (Ellgaard et al., 1999).

2. The link between ageing and cellular senescence

Cellular senescence, which can be induced by various stresses, has been implicated in development, wound healing, tissue repair and ageing (Campisi, 2013; Campisi and Robert, 2014; Demaria et al., 2014a; Munoz-Espin and Serrano, 2014; van Deursen, 2014b; Velarde et al., 2013). It may lead to different outcomes – suppression of malignancy or acceleration of ageing—depending on the context and persistence of senescent cells *in vivo* (Campisi, 2013; Campisi and Robert, 2014; Munoz-Espin and Serrano, 2014; van

Deursen, 2014b). The hallmark of cellular senescence is an irreversible arrest of cellular proliferation. The main pathways that lead to this cell cycle arrest are governed by two tumor suppressor axes: the p53-p21 axis and the p16^{INK4a}-pRB axis. Importantly, rather than a finite static end point, the senescent state is complex and dynamic due to a senescence-associated secretory phenotype (SASP)—the secretion by senescent cells, of a suite of cytokines, growth factors and proteases that promote tissue repair and regeneration or inflammation (Campisi, 2013; Demaria et al., 2014b; Muñoz-Espín and Serrano, 2014). The SASP is a plastic phenotype, and its composition varies with genotype, cell type and senescence stimulus. It is now well established that senescent cells accumulate during ageing (Adams, 2009; Bernardes de Jesus and Blasco, 2012; Campisi, 2011; Lopez-Otin et al., 2013; Muñoz-Espín and Serrano, 2014; Sharpless and Sherr, 2015; van Deursen, 2014a) and are involved in many age-related pathologies, including cancer (Campisi, 2013; van Deursen, 2014a). The primary reason for this 'dark side' of cell senescence is that the chronic presence of senescent cells and a persistent SASP cause local and systemic inflammation, which fuels a variety of age-related diseases. Evidence for this has been obtained in a number of mouse models (Baker et al., 2011; Campisi, 2013; Campisi and Robert, 2014; Kennedy et al., 2014; Zhu et al., 2015). Among the most potent inducers of the SASP are genotoxic stresses and conditions that lead to persistent DNA damage signaling (Kang et al., in press; Rodier et al., 2011). Indeed, several DNA damage response (DDR) players are involved in establishing and maintaining the SASP (Rodier et al., 2009b). Thus, the senescence response, and particularly the SASP, is a strong candidate for linking ageing phenotypes and age-related rises in genotoxic stress (Maslov et al., 2013; Vijg and Campisi, 2008).

3. Similarities and differences between brain ageing and brain neurodegeneration

The progressive decline in physiological functions that characterizes ageing is clearly manifested in the central nervous system (CNS), where it affects all of its functions. Brain degenerative diseases (BDDs) as well as ageing of the brain lead to impairment of brain functionality. Brain functionality is defined as the global input/output processing controlled by coordinated activation of the neural circuits in inter- and intra-hemisphere networks. Brain functionality is not totally impaired in BDDs or the ageing brain; rather, the activity of specific circuits in certain networks is abrogated, affecting topological organization, cell numbers, cellular functionality, and the communication among distinct circuits. At the cellular level, it was noticed that not all cell types in the CNS are affected equally by the ageing process (Drachman, 2006; Pakkenberg et al., 2003; West et al., 1995). These similarities raise the question whether BDDs actually reflect segmental ageing of the brain. Notably, the risk for developing BDD rises with age: beyond the age of 65 years the risk of Alzheimer's disease (AD) doubles every 5 years, and at age 85 the incidence of AD is 20-fold higher than at 65 (Bachman et al., 1993).

After the age of 50, brain weight declines by about 2–3% per decade (Esiri et al., 1997). This decline gradually accelerates, and after 80, brain weight has typically decreased by 10% compared to previous highest weight. Between young adulthood to the 9th decade, frontal lobe volume decreases by about 12% and temporal lobe volume by 9%, while parietal and occipital lobes show little tissue loss; this process largely occurs after age 50 (DeCarli et al., 2005). In addition to macroscopic changes, brain ageing is also associated with cellular and molecular changes: by the age of 90, nearly 10% of the average 2×10^9 neocortical neurons are lost (Pakkenberg et al., 2003), and according to hypothetical calcula-

tions, during this decline the human brain loses about one neuron per second. BDDs may accelerate this process significantly (Stark et al., 2007). Notably, neurons are not lost uniformly throughout the brain; for example, the number of neurons in the hippocampal complex decreases little, if any, during normal ageing (West et al., 1995), despite the decline of hippocampal volume (Scahill et al., 2003) and some neuronal loss in the entorhinal cortex (Lippa et al., 1992).

A decreased numbers of functioning synapses and disturbed stimulation of synaptic plasticity were observed in the ageing brain (Dorszewska, 2013). Dendritic arbors and synaptic spines of cortical pyramidal neurons undergo age-related regressive changes in specific regions (Duan et al., 2003; Hof and Morrison, 2004). The number and the density of synaptic spines decrease more than 45% in brains after age 50 compared to younger individuals (Jacobs et al., 1997). Other cellular process also play a role in brain ageing: enzymes that synthesize neurotransmitters such as dopamine, noradrenaline and acetylcholine decrease with age (Carlsson, 1987); cellular senescence is observed mainly in neural stem cells and glial and endothelial cells (Ferron et al., 2004; Rodriguez-Arellano et al., 2015; Streit, 2006; Streit and Xue, 2013; Thorin-Trescases et al., 2005); telomere shortening was seen mainly in mouse neural stem cells (Ferron et al., 2004)as well as human neural precursor cells (Ostenfeld et al., 2000) and age-dependent depletion of neuronal stem cells results in decreased neurogenesis in human brain (Drachman, 2006); and reduced levels of neurotrophic factors such as BDNF and NT3 were implicated in brain ageing (Duman, 2005).

Evidence is mounting of stochastic accumulation of damage to cellular macromolecules, including DNA, RNA, proteins and lipids, in the ageing or degenerating brain (Maynard et al., 2015b). Mitochondrial dysfunction is observed in the ageing brain and as a core feature of several BDDs. Notably, this dysfunction is accompanied by accumulating damage to mitochondrial DNA (Keogh and Chinnery, 2015; Szczepanowska and Trifunovic, 2015). It was argued that stochastic drifts in variegated gene expression are major contributors to differences in the pace and patterns of ageing among members of the same species. Such drifts may be responsible for the quasi-stochastic distribution of geriatric pathologies, including the "big three" of AD, atherosclerosis, and increased incidence of cancer (Martin, 2012). It was also claimed that transcriptional error rate increases in ageing neurons, leading to production of aberrant proteins (van Leeuwen et al., 1998). It was shown that ageing impacts on cell respiration, leading to overproduction of reactive oxygen species (ROS), and this process was tied to activation of cell death pathways (Campos et al., 2014; Stoll et al., 2011). Proteins are major targets of reactive oxygen and nitrogen species (ROS/RNS), and the resultant modifications lead to structural and functional modifications of these molecules. Thus, the impact of oxidative/nitrosative stress on cellular macromolecules, mainly proteins and lipids, is considered a contributing factor to both ageing and degenerative processes and the associated diseases (Butterfield and Dalle-Donne, 2012; Butterfield et al., 2012).

In contrast to younger brains, the microglia in the ageing brain respond to activation of the immune system triggered by infection or surgery with elevated and prolonged production of pro-inflammatory cytokines such as interleukin-1β and reduced levels of BDNF. This elevated inflammatory response can compromise processes critical for optimal cognitive functioning (Cortese et al., 2011; Patterson, 2015). Brain ageing in rats was found to be associated with increased permeability of the blood-brain barrier (BBB), and it was suggested that infiltration of monocytes contributes to elevation of ROS levels in the ageing brain (Blau et al., 2012; Enciu et al., 2013). Higher levels of CD11b+ and CD45 cells—markers of microglia activation—were also detected in the ageing brain. Likewise, expression levels of chemotactic molecules, such as interferon-inducible protein 10 (IIP10) and monocyte chemotactic protein-1(MCP-1), are increased in the hippocampal region in the ageing brain of rats (Blau et al., 2012).

4. The DNA damage-neurodegeneration-ageing connection

Genome instability is among the 'hallmarks of ageing' (Lopez-Otin et al., 2013), and maintenance of genome integrity is considered an important genetic factor in determining ageing pace (Cho and Suh, 2014; Lopez-Otin et al., 2013; Maynard et al., 2015a; Vijg, 2014; Vijg and Suh, 2013) (Fig. 1). The most serious threat to genome stability is damage inflicted on the DNA molecule (Lindahl, 1993). While DNA damage is usually mentioned in connection with environmental agents, most of the ongoing damage to the cellular genome—some tens of thousands of lesions each day—is caused by endogenous oxygen radicals produced during normal metabolism (Cadet and Wagner, 2013; Lindahl, 1993). The defense systems that guard cells against these ongoing threats to genome stability are critical for cellular homeostasis, pre- and postnatal development, and the prevention of premature ageing and age-related pathologies, including cancer and degenerative diseases (Abbas et al., 2013; Maynard et al., 2015a; Vijg and Suh, 2013). These systems respond to DNA lesions by activating specific DNA repair mechanisms, which repair a variety of DNA base lesions, base-pair mismatches, crosslinks, and single- and double-strand breaks (Ciccia and Elledge, 2010). DNA repair is, however, just one arm of the broad DDR—an elaborate signaling network that swiftly modulates many physiological processes, constituting one of the most comprehensive cellular responses to a physiological stimulus (Sirbu and Cortez, 2013).

The relationship between genome stability and human health is best illustrated by many genome instability syndromes that are typically characterized by progressive degeneration of specific tissues, cancer predisposition, chromosomal instability, and hypersensitivity to DNA damaging agents (Maynard et al., 2015a; O'Driscoll, 2012). Predisposition to specific cancers is conferred by heterozygosity for mutations that inactivate certain DDR players, such as BRCA1, BRCA2, p53, and the mismatch repair proteins (Pena-Diaz and Jiricny, 2012; Roy et al., 2012; Sorrell et al., 2013). It is becoming evident, however, that variations in DDR efficiency contribute not only to the development of cancer, but also to metabolic and cardiovascular diseases (Ishida et al., 2014; Shimizu et al., 2014). In fact, different combinations of sequence alterations in DDR genes may account for a continuum of variation in genome stability in the human population that affects public health on a large scale. This variation gives rise to hidden phenotypes that develop in apparently healthy individuals and are considerably milder and develop more slowly than the overt genome instability syndromes. Information about these conditions is scant, being based on sporadic reports, but it is clear that individual differences in maintaining genome stability are responsible for a substantial part of the immense variation in ageing and associated diseases (Burgess et al., 2012; Karakasilioti et al., 2013; Lopez-Otin et al., 2013; Maynard et al., 2015a; Shadyab and LaCroix, 2015; Vijg and Suh, 2013; Wolters and Schumacher, 2013). This is vividly exemplified by the segmental (tissue-specific), accelerated ageing observed in several genome instability syndromes in humans and mouse models of DNA repair deficiencies, particularly in mice with acute deficiencies in the nucleotide excision repair (NER) pathway (Borgesius et al., 2011; Cleaver et al., 2009; de Waard et al., 2010; Diderich et al., 2011; Dolle et al., 2011; Gregg et al., 2011; Jaarsma et al., 2011; Maslov et al., 2013; Maynard et al., 2015a; Schumacher et al., 2008; Vermeij et al., 2014).

A new insight into the role of persistent DNA damage in ageing was obtained from recent studies that showed that nuclear
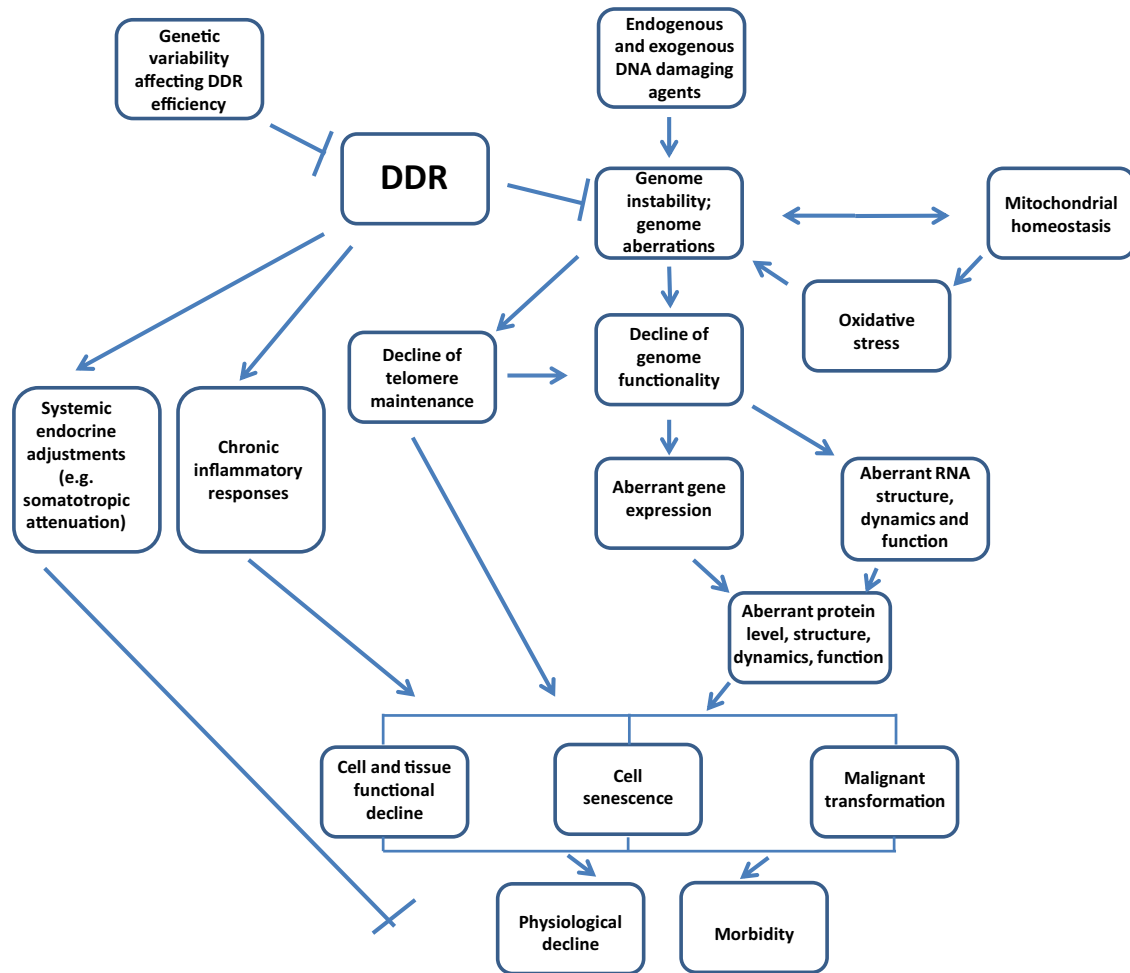
Fig. 1. A scheme depicting the effect of variation in DDR efficiency and genome stability on ageing and associated morbidity.

DNA damage signals to the mitochondria as part of the nuclear-mitochondrial (NM) signalling (reviewed by (Fang et al., 2016)). Reduction in mitochondrial function and homeostasis has long been noticed in ageing (Ahlqvist et al., 2015; Lopez-Otin et al., 2013; Pinto and Moraes, 2015). A key molecule in NM signalling is NAD^+ (Mouchiroud et al., 2013), whose decline upon persistent DNA damage leads to aberrant NM signalling and reduced levels of oxidative phosphorylation players in mitochondria (Gomes et al., 2013).

Recognition of the breadth and power of the DDR signaling network has come mainly from studies of the response to the DNA double-strand break (DSB), an extremely harmful DNA lesion that vigorously activates the DDR (Thompson, 2012). DSBs are induced by ionizing radiations, radiomimetic chemicals, and endogenous reactive oxygen species (ROS) (Schieber and Chandel, 2014). They also accompany physiological genomic transactions such as meiotic recombination (Borde and de Massy, 2013; Lange et al., 2011) and the rearrangement of antigen receptor genes in the adaptive immune system (Alt et al., 2013). DSBs are ultimately repaired via nonhomologous end-joining (NHEJ), or homologous recombination repair (HRR) mediated by recombination between sister DNA molecules, with tight control of the delicate balance between these repair pathways (Chapman et al., 2012; Jasin and Rothstein, 2013; Radhakrishnan et al., 2014; Shibata and Jeggo, 2014). However, DSB repair constitutes just one branch of the larger DSB response, which also activates special cell cycle checkpoints, modulates gene expression, alters protein turnover and activity, and affects many other cellular circuits. This extensive network is based

on a group of *bona fide* DDR players, but it also temporarily recruits numerous players from other arenas of cellular metabolism to the DDR where they undergo specific post-translational modifications (PTMs) (Goodarzi and Jeggo, 2013; Panier and Durocher, 2013; Polo and Jackson, 2011; Shiloh and Ziv, 2013; Sirbu and Cortez, 2013; Thompson, 2012). The chief mobilizer of the DSB response is the protein kinase ATM (Guleria and Chandna, 2015; McKinnon, 2012; Shiloh and Ziv, 2013), whose activity is markedly enhanced in response to DSB induction (Paull, 2015). ATM then proceeds to phosphorylate a plethora of key players in various damage response pathways (Bensimon et al., 2010; Matsuoka et al., 2007). ATM belongs to a family of PI-3 kinase-like protein kinases (PIKKs) (Baretic and Williams, 2014; Lovejoy and Cortez, 2009). This family includes, among others, the catalytic subunit of the DNA-dependent protein kinase (DNA-PKcs), which is involved in the NHEJ pathway of DSB repair and probably also in other genotoxic stress responses (Chen et al., 2012; Kong et al., 2011), and ATR, which responds primarily to stalled replication forks (Errico and Costanzo, 2012; Marechal and Zou, 2013). Evidence suggests a considerable degree of redundancy and collaboration between these three PIKKs, which preferably phosphorylate Ser or Thr residues followed by Gln (S/TQ motif) (Gobbini et al., 2013; Lovejoy and Cortez, 2009; Marechal and Zou, 2013; Sirbu and Cortez, 2013; Thompson, 2012).

ATM might also be involved in many DNA repair pathways and other aspects of genome stability by virtue of its ability to phosphorylate key components in these pathways (Shiloh, 2014), in addition to its cardinal role as the mobilizer of the DSB response. Impor-

tantly, ATM emerged recently as a homeostatic protein kinase that is also active in other stress responses and several metabolic pathways. Notable among them are maintenance of the cellular redox balance, mitochondrial homeostasis, and peroxisome-associated autophagy (Boohaker and Xu, 2014; Guleria and Chandna, 2015; Shiloh and Ziv, 2013; Zhang et al., 2015).

ATM loss due to null mutations in the *ATM* gene (Savitsky et al., 1995) leads in humans to the autosomal recessive disorder, ataxia-telangiectasia (A-T)—a prototypic genome instability syndrome (Perlman et al., 2012). A-T is characterized by severe neuromotor dysfunction emanating primarily from progressive cerebellar atrophy, telangiectasia (dilation of blood vessels observed primarily in the eyeballs), immunodeficiency, sterility, predisposition to lymphoid malignancies, and extreme sensitivity to ionizing radiation. The cellular phenotype of A-T is characterized by chromosomal instability, premature senescence of cultured primary fibroblasts, and hypersensitivity to DNA damaging agents, particularly those that induce DSBs (Shiloh, 1995).

There is growing recognition of the premature ageing aspects of A-T (Shiloh & Lederman, submitted). Notably, later symptoms that emerge in A-T patients during the second and third decade of life are type-2 diabetes, hyperlipidemia, metabolic syndrome, liver inflammation and cirrhosis, osteoporosis, and solid tumors, suggesting segmental premature ageing as part of the disease phenotype. Carriers of A-T mutations also raise the issue of accelerated ageing. While cancer predisposition of the carries is debated (Thompson et al., 2005), two reports indicate increased deaths from ischemic heart disease among A-T carriers (Su and Swift, 2000; Swift and Chase, 1983); more overt segmental ageing is seen in A-T patients; and A-T fibroblasts exhibit premature senescence (Shiloh et al., 1982). These observations collectively link reduction in ATM levels to enhanced ageing.

A-T is a prime example of a human genome instability disorder linking defective DDR, brain degeneration and premature ageing. The link between genome instability and brain degeneration is also demonstrated by several other autosomal recessive syndromes resulting from deficiencies in DNA repair enzymes (Gilmore, 2014; Madabhushi et al., 2014; McKinnon, 2013; Rulten and Caldecott, 2013). Interestingly, these syndromes affect primarily the cerebellum, similar to A-T. Prominent disorders in this group are ataxia with oculomotor apraxia 1 (AOA1) resulting from aprataxin (APTX) deficiency; ataxia with oculomotor apraxia 2 (AOA2) resulting from senataxin (SETX) deficiency; and spinocerebellar ataxia with axonal neuropathy (SCAN1) resulting from tyrosyl-DNA phosphodiesterase 1 (TDP1) deficiency (Gilmore, 2014; Madabhushi et al., 2014; McKinnon, 2013; Rulten and Caldecott, 2013). Recently, deficiency of tyrosyl-DNA phosphodiesterase 2 (TDP2) was identified in individuals with intellectual disability, seizures and ataxia (Gomez-Herreros et al., 2014), and partial loss of polynucleotide kinase 3′-phosphatase (PNKP) was reported to lead to a progressive brain degenerative syndrome involving marked cerebellar atrophy (Oegema et al., 2014; Poulton et al., 2013). APTX, TDP1, and TDP2 are involved in processing DNA strand termini associated with single-strand breaks (SSBs) caused by different mechanisms (Ahel et al., 2006; Pommier et al., 2014; Tumbale et al., 2014), and PNKP processes abnormal termini in SSB and DSB repair (Weinfeld et al., 2011). SETX was recently implicated in resolving RNA:DNA hybrid molecules (such as R-loops) (Richard et al., 2013; Yuce and West, 2013), which occur when transcription is disturbed and lead to genomic instability (Chan et al., 2014; Gaillard et al., 2013; Hamperl and Cimprich, 2014). This suggests that the ATM function whose loss contributes to the cerebellar atrophy in this disease is ATM's supportive role in many DNA repair pathways other than DSBs (Shiloh, 2014).

5. Systems interaction in genome instability-associated ageing

Genome instability affects an array of cell-autonomous as well as recently uncovered systemic signaling pathways that impinge on ageing. Results from mouse models that age prematurely due to NER defects, and equivalent models based on the nematode *C. elegans*, established intriguing links between unrepaired DNA lesions and pathways that regulate longevity (Garinis et al., 2009; Mueller et al., 2014). NER-deficient mouse models of the human progeroid syndromes, Cockayne syndrome (CS), trichothiodystrophy (TTD) and ERCC1-XPF-Progeria (XFE), mimic the accelerated ageing process observed in the human patients (Niedernhofer et al., 2006; van de Ven et al., 2006; van der Pluijm et al., 2007). Transcriptome analysis of the mutant progeroid animals revealed a high degree of similarity to gene expression patterns of naturally ageing wild-type mice, suggesting that accumulating DNA damage is involved in the ageing process in wild-type animals (Schumacher et al., 2008). Furthermore, transcriptomes of the progeroid mutants showed similarity to those of mice with extended longevity due to either calorie restriction or mutations that inactivate the somatotropic axis; indeed, the progeroid mutants exhibited attenuation of the somatotropic axis. This axis is mediated by pituitary growth hormone (GH) that activates the GH receptor (GHR) in peripheral tissues, leading to secretion of insulin-like growth factor 1 (IGF-1) into the circulation, which mediates cellular growth and survival signaling through the IGF-1 receptor (IGF-1R). As humans age, IGF-1 and GH levels decline, resulting in a growth-deprived endocrine environment (Carter et al., 2002). However, constitutive dampening of the somatotropic axis due to pituitary defects in various mouse mutants leads to a significant extension of lifespan (Bartke, 2009). The IGF-1 pathway indeed comprises a highly conserved pathway of longevity (Di Bona et al., 2014; Kenyon, 2005; O'Neill et al., 2012).

Human and murine cells respond to persistent DNA damage by attenuation of the GHR and IGF-1R that leads to enhanced cellular stress resistance (Garinis and Schumacher, 2009). It was proposed that somatotropic attenuation counteracts the detrimental consequences of accumulating DNA damage with ageing by enhancing tissue maintenance and reducing cellular proliferation (Schumacher, 2009). However, it is conceivable that the systemic consequences of reduced GH/IGF-1 endocrine signaling might affect different tissue types in different ways. For example, reduced IGF-1R could protect neurons in a mouse model of Alzheimer's disease (Cohen et al., 2009). In contrast, IGF-1 supplement could overcome the postnatal growth defect in a mouse model of Hutchinson-Gilford-Progeria-syndrome (Marino et al., 2010). While many cancer types are dependent on IGF-1R-mediated signaling, the reduced mitogenic signaling might also impair tissue renewal. Indeed, the endocrine environment in progeroid Sirt6- or telomerase-deficient animals could not support engraftment of hematopoietic stem cells (Mostoslavsky et al., 2006; Song et al., 2010). The complexity of the consequences of genome instability in mammalian physiology raised the necessity to establish mechanisms of insulin-like signaling (IIS) responses to DNA damage in a simple metazoan system. Thus, it was shown that in *C. elegans*, the FOXO homolog DAF-16-the critical downstream effector that is negatively regulated by IIS—is activated upon persistent DNA damage, overcoming the developmental growth arrest and promoting tissue maintenance and longevity amid persistent DNA damage (Mueller et al., 2014). It was proposed that longevity assurance mechanisms such as DAF-16 activation could raise the threshold of DNA damage-driven functional decline (Ribezzo et al., 2016) (Ribezzo et al. Semin in Cancer 2016).

The importance of systemic adjustments during human ageing is also evident in the endocrine alterations—such as reduced circu-

lating growth factors including GH and IGF-1-that are controlled by complex feedback loops that are centrally and peripherally regulated. It is, therefore, crucial to understand how the DDR operates on a systemic level. Evidence from the simple metazoan *C. elegans* recently showed that a "germline DNA damage-induced systemic stress resistance" (GDISR) is mediated by an innate immune response triggered upon genome instability in germ cells. Consequently, GDISR leads to elevated endurance of somatic tissues through activation of the ubiquitin proteasome system (Ermolaeva et al., 2013). It will be highly interesting to determine how the complex hormonal interactions between the human germline and central and peripheral tissues might be affected by genome instability in the germ cells.

Immune responses to DNA damage also play an important, albeit incompletely understood, role in mammals: for example, the local inflammation triggered by UV-induced DNA damage is antagonized by a systemic immunosuppression mediated by T-regulatory cells that are activated when Langerhans cells migrate from the damage site in the skin to the lymph nodes (Schwarz and Schwarz, 2011). In addition, the cytokines secreted by senescent cells in the SASP process might trigger tissue inflammation with ageing (Muñoz-Espín and Serrano, 2014). Thus, while the cytokines released by these cells might promote growth of surrounding cancer cells, they might also contribute to removal of senescent cells by activating immune cells (Chinta et al., 2014; Rodier et al., 2009a; Xue et al., 2007). It is thus becoming evident that the DDR has paracrine and endocrine consequences, and inflammatory responses to DNA damage might play an important part in causing tissue degeneration and accelerating tissue ageing (Osorio et al., 2012; Tilstra et al., 2012).

6. The effect of malfunctioning DDR on brain functionality: focus on Atm and Nbn

A-T is unique among the genome instability syndromes leading to brain degeneration, in view of the pleiotropic role of ATM in cellular physiology. While ATM's role in the DSB response is its most extensively studied function, ATM recently emerged as a homeostatic protein kinase that is active in other stress responses and in several metabolic pathways. Notable among them are maintenance of the cellular redox balance (Cremona and Behrens, 2014; Ditch and Paull, 2012; Guleria and Chandna, 2015; Semlitsch et al., 2011; Yang et al., 2011), and mitochondrial metabolism including maintenance of mitochondrial DNA and autophagy of peroxisomes (pexophagy) (Ambrose and Gatti, 2013; Eaton et al., 2007; Sharma et al., 2014; Valentin-Vega and Kastan, 2012; Valentin-Vega et al., 2012; Zhang et al., 2015). Importantly, some of these functions involve different modes of ATM activation that may direct ATM to different substrates (Ditch and Paull, 2012; Guo et al., 2010). The evidence that ATM's capacity as a protein kinase is exploited in signaling pathways that are not associated with DNA damage, some of them cytoplasmic (Ambrose and Gatti, 2013; Ditch and Paull, 2012; Eaton et al., 2007; Herrup, 2013; Yang et al., 2011; Zhang et al., 2015), adds fuel to the ongoing debate about the cause of the brain degeneration in A-T (Biton et al., 2008; Ditch and Paull, 2012; Hoche et al., 2012; Yang et al., 2014). Investigators have suggested that the lost ATM functions responsible for the cerebellar atrophy in A-T could be the same ones associated with ATM's 'non-DDR' roles (Ditch and Paull, 2012; Eaton et al., 2007; Herrup, 2013; Herrup et al., 2013; Kim et al., 2010; Li et al., 2012, 2013; Yang et al., 2014). Among other observations, it was found that ATM plays a role in epigenetic dynamics in neurons, which is unrelated to DNA damage (Herrup, 2013; Herrup et al., 2013; Jiang et al., 2015; Li et al., 2013). While this discussion continues, it should be borne in mind that the common denominator of A-T and the above cerebellar ataxias is defective handling of DNA damage. This leaves us with major ques-

tions: how does genome stability impact so harshly on the brain? What are the cell types in the brain for which genome instability is particularly critical? Many studies attempting to answer these questions have focused on the cerebellum, in which ATM loss is most critical.

These studies are usually based on the mouse model of A-T—the *Atm*-knockout mouse, which recapitulates most A-T symptoms with the exception of the severe progressive brain degeneration (Barlow et al., 1996; Borghesani et al., 2000; Elson et al., 1996; Xu et al., 1996). Minor neurological abnormalities including decrease in electrophysiological activity of neurons were, however, noticed in these animals (Borghesani et al., 2000; Chiesa et al., 2000; Kuljis et al., 1997), suggesting that, if given enough time, a distinct neurological phenotype might develop in the animals (in human A-T patients the cerebellar atrophy culminates at 8–10 years of age). Importantly, the phenotypic similarity between A-T, AOA1, AOA2 and SCAN1 is reflected in the corresponding mouse models, which were generated by knocking out the corresponding murine genes (*Atm*, *Aptx*, *Setx* and *Tdp1*, respectively): in all of them, the sensitivity to specific DNA damaging agents is recapitulated by the animal, but not the human cerebellar degeneration (Becherel et al., 2013; El-Khamisy et al., 2009; Gomez-Herreros et al., 2013, 2014).

A mouse model that does exhibit cerebellar atrophy was obtained by conditionally knocking out a single gene in the DDR: the *Nbn* gene in the murine nervous system (*Nbn*-Δ-CNS) (Frappart et al., 2005; Yang et al., 2006). This gene encodes the murine protein Nbs1, the ortholog of human NBS1. This protein is a member of the MRE11-RAD50-NBS1 (MRN) complex—a central DSB sensor (Paull and Deshpande, 2014; Stracker and Petrini, 2011) that is required for ATM activation by DSBs (Falck et al., 2005; Uziel et al., 2003). In humans, hypomorphic mutations in the *NBN* gene cause the Nijmegen breakage syndrome (NBS), which features radiosensitivity, chromosomal instability, cancer predisposition, microcephaly and mental retardation (Digweed and Sperling, 2004). The *Nbn*-Δ-CNS animals exhibit a dramatic neurological phenotype that combines the microcephaly typical of human NBS patients with proliferation arrest of granule cell progenitors and apoptosis of post-mitotic neurons in the cerebellum, leading to severe ataxia (Frappart et al., 2005). Additional facets of this phenotype are increased areas of white matter in the brain, defective myelin formation and quality, defective oligodendrocyte development (Assaf et al., 2008; Liu et al., 2014), and a profound defect in the integrity and functionality of glial cells (Galron et al., 2011). This phenotype may be explained by the comprehensive role of the MRN complex in the DDR (including its requirement for ATM activation), and shows that a cerebellar phenotype *can* be induced in the mouse by severely compromising the DDR. The *Atm*-knockout and the *Nbn*-Δ-CNS mouse models will serve us in the following discussion.

It is highly likely that information processing in the brain is not carried out at the level of single neurons but rather at a system level, exemplified by the dynamics of neural-glial networks (Levine-Small et al., 2011; Potter, 2001; Segev et al., 2004, 2002, 2003; Segev and Ben-Jacob, 2001; Wheeler and Brewer, 1994). Using microelectrode arrays as a tool to simultaneously record the output of many neurons, Levine-Small et al. (Levine-Small et al., 2011) found reduced synchronization persistence in Atm-deficient neurons compared to wild-type synchronization, after chemically imposed DNA damage. This work highlighted a defect at the level of neural networks in the murine Atm-deficient brain and pointed to the effect of Atm loss on the brain as a system of communicating cells.

The visual system is an integral part of the CNS, and the DNA of retinal neurons is probably exposed to considerable levels of ROS due to their extremely high metabolic activity (Yu and Cringle, 2001). These neurons are highly dependent on glial-vascular support. Examination of the retinas of Atm-deficient mice revealed
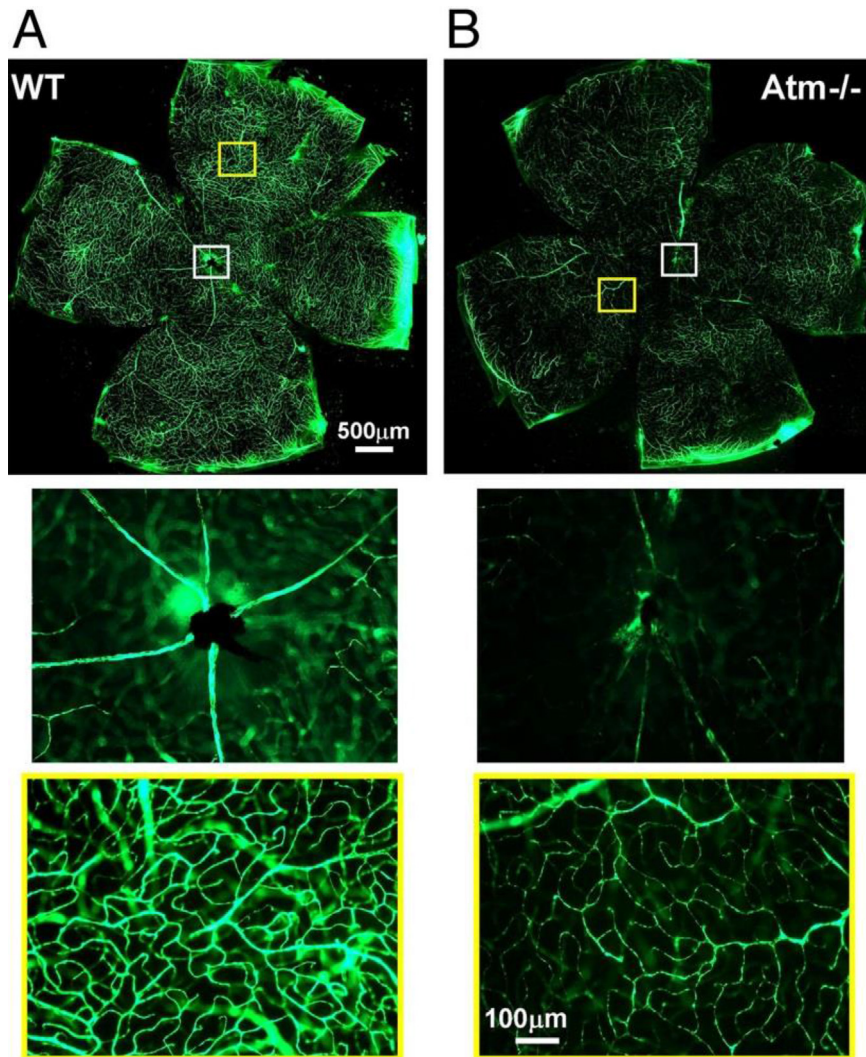
Fig. 2. Attenuated blood vessels in retinas of $Atm^{-/-}$ mice (Raz-Prag et al., 2011). Flat-mount retinas of 2-month-old WT (A, n = 5) and $Atm^{-/-}$ (B, n = 5) mice imaged with a fluorescent microscope following intracardial intracra perfusion with dextran-fluorescein. Insets show larger magnification of optic nerve region (white frame**)** and typical peripheral region (yellow frame**).** (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

reduced integrity of the retinal vasculature (Fig. 2), increased levels of vascular endothelial growth factor (VEGF), fibrinogen, and reduced levels of cell adhesion molecules such as occludin. Consequently, retinal micro-hemorrhages were observed. Morphological alterations in glial cells were also observed in *Atm-/-* retinas. Electroretinographic (ERG) examination revealed amplitude aberrations in 2 month-old *Atm-/-* mice, which progressed to significant functional deficits in the older animals. The results suggested that impaired vascularization and astrocyte-endothelial cell interactions in the central nervous system may be part of the A-T phenotype and may aggravate the neurological symptoms of this disease (Raz-Prag et al., 2011).

Brain functionality is highly dependent on proper function of its astrocytes (Barzilai, 2013; Meshulam et al., 2012) (Fig. 3). The -Nbn-Δ-CNS mouse exhibits severe cerebellar atrophy and reduced number of Purkinje cells (Frappart et al., 2009). It was found that this animal model exhibits reduced levels of both cerebellar granule neurons and microglial cells, and reduced number of markers of astrocyte functionality, such as glutamine synthetase, BDNF and NT3 (Galron et al., 2011).

7 Glial cells: central players in brain homeostasis and functionality

Until recently, brain function was thought to be solely dependent on the function of neurons, and brain degenerative disorders were considered diseases of neurons. Thus, investigation of the neurological phenotype of A-T focused on Purkinje neurons, granule neurons and dopaminergic neurons, while other CNS cells received less attention (Barzilai et al., 2008). Only recently have the important physiological functions of glial cells been studied extensively (Table 1)(Haydon and Carmignoto, 2006). Importantly, the relative number of glial cells in the human brain is more than 10 times greater than in lesser mammals, and astrocytes display a much greater complexity in higher primates than, say, in rodents. Thus, it has been estimated that a human protoplasmic astrocyte contacts and enwraps ~2 million synapses compared to ~100,000 synapses in mouse astrocyte (Oberheim et al., 2006). Human protoplasmic astrocytes manifest a threefold larger diameter and have tenfold more primary processes than those of rodents (Oberheim et al., 2006), in contrast to neuronal cells, whose morpho-physiological complexity differs very little between humans and other mammals. For example, the density of synaptic
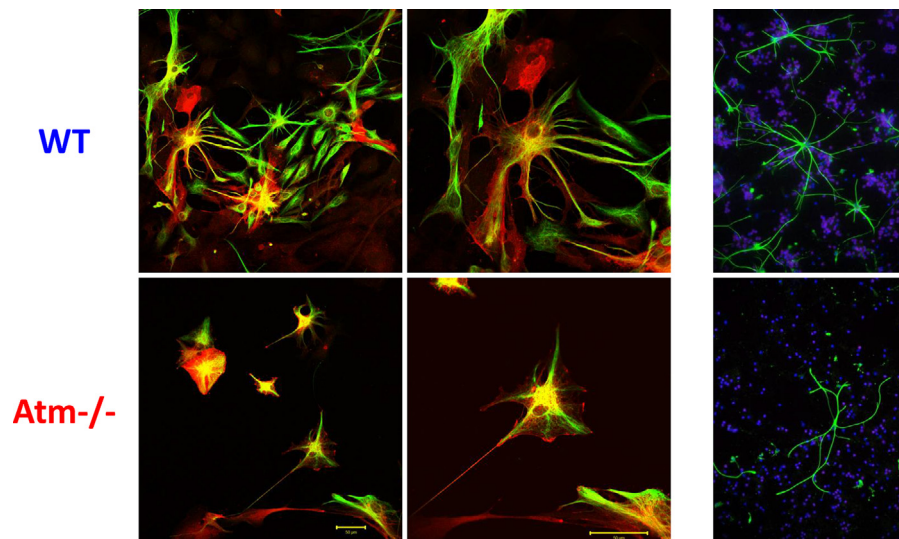
Fig. 3. Abnormal appearance of cultured cortical cerebellar astrocytes from Atm-deficient mice. Left panel: Astrocytes were isolated form 2-month-old animals and grown in culture for 2 weeks. The cultures were stained with antibodies against Ezrin (red) and glial fibrillary acidic protein (GFAP) (green, astrocytic marker). Right panel: cerebellar cultures enrich for granule neurons and astrocytes were isolated from 8-days old mice and grown for 2 weeks. The cultures were stained with NeuN (red, neuronal marker) and GFAP (green). Note the reduced number and length of astrocytic processes in Atm-deficient cells (R. Galron, unpublished data). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1

Importance of astroglial cells in brain functionality and homeostasis. Astroglial cells have a variety of critical functions ranging from metabolic control to regulation of the brain vascular system, to buffering the levels of various electrolytes and preventing oxidative stress. The ability of astrocytes to maintain brain homeostasis is hampered in various pathological conditions. The severity of brain degeneration and the rate of its ageing are closely associated with the degree of astroglial malfunction.

Normal physiological conditions	Pathological conditions involving malfunction of astroglial cells
Homeostasis of gliotransmitter release	Excitoxic transmitter release
Control of water distribution	Edema
Metabolic control of the neurovascular unit	Malfunctioning metabolism in neurons
ROS scavenging	Excessive ROS release such as NO and hydrogen peroxide
K^+ buffering	Excessive K^+ release
Growth and trophic factor release	Reduced growth and trophic factor support
Regulation of synaptogenesis and pruning	Malfunctioning synaptogenesis and pruning
Maintenance of the blood-brain barrier	Malfunctioning blood-brain barrier
Conversion of glutamic acid to glutamine in neurotransmission via glutamine synthetase activity	Reduced conversion of glutamic acid to glutamine

contacts in the brains of rodents and humans is roughly similar: 1-1.4×10^9 mm^{-3} (Oberheim et al., 2006).

It is now evident that glial cells (especially astroglial) are as diverse as neurons (Emsley and Mackli, 2006; Oberheim et al., 2012). They shape the micro-architecture of the brain matter, and are capable of expressing many of the same receptors and channels as neurons. They respond to synaptic inputs, are organized as communicating networks, release gliotransmitters that enable long-range information exchange, and can act as pluripotent neural precursors capable of adult neurogenesis (Buffo et al., 2008). Astroglial cells functionality is critical to CNS homeostasis. Under normal physiological conditions, they buffer extracellular K^+ concentrations, regulate neurotrophic factors release, and control extracellular concentrations of neurotransmitters released from neighboring synapses. In addition, astrocytes regulate water movement and distribution and are capable of neutralizing ROS in the neighboring cells. Astrocytes lend major metabolic support to adjacent neurons by absorbing glucose from nearby blood vessels, converting it to lactate, and providing it to neurons. Astrocytes are also involved in the regulation of synaptogenesis, synaptic maturation, synapse elimination (Chung et al., 2013), neurotransmitter homeostasis, brain microcirculation, and control of formation and maintenance of the blood–brain barrier (BBB) (Abbott et al., 2006; Anderson and Nedergaard, 2003; De Keyser et al., 2003; Dong and Benveniste, 2001; Gordon et al., 2007; Haydon, 2001; Ke et al., 2001; Nase et al., 2008; Nedergaard et al., 2003; Nedergaard and Verkhratsky, 2012; Risher et al., 2009; Stevens, 2008; Verkhratsky et al., 2014; Zonta et al., 2003). Thus, astrocytes are active partners in synaptic function, integrating and processing synaptic information and influencing synaptic transmission and plasticity (Perea et al., 2009; Verkhratsky et al., 2016).

These processes depend, to a large extent, on how astrocytes communicate with surrounding cells. They do so via plasma membrane channels, receptors, transporters, and mechanisms that mediate the exchange of molecules by exo- and endocytotic processes (Gucek et al., 2012; Kreft et al., 2004; Osborne et al., 2009; Parpura et al., 2011, 2012; Parpura and Zorec, 2010; Zorec et al., 2012). Therefore, rather than looking at isolated neuronal networks, the glial-neuronal networks have to be considered. These advances in 'gliobiology' are challenging the "neuron doctrine" that focuses solely on neurons, and are fundamentally reshaping our perception of brain organization: the result is a more inclusive theory of brain function. Importantly, dysfunctional neuron-glia communications may play a major role in BDDs including those caused primarily by genome instability.

Under metabolic stress, astrocytes release ROS and NO, which may generate toxic radicals such hydroxyl radical and peroxynitrite. Malfunctioning astrocytes fail to regulate water movement and distribution, thereby contributing to the generation of edema. Under pathological conditions, the glutamine synthetase (GS) activity of astrocytes is reduced (Galron et al., 2011; Sofroniew and Vinters, 2010); once such that they can no longer recycle

glutamine back to synapses for reconversion into the active transmitter glutamate, and high levels of glutamate are released which lead to cytotoxicity by elevating the intracellular levels of Ca^{2+}. Failure to buffer extracellular K^+ concentrations promotes further over-excitation of neuronal cells and the glial cells secrete pro-inflammatory factors in conjunction with ROS, further exacerbating CNS damage (Barzilai, 2011).

8. Ageing and DNA damage: effects on the functionality of astroglial cells

Degenerative changes in the ageing brain include synaptic loss and white matter atrophy, gradual increase of oxidative, proteotoxic and metabolic stresses, and low-level chronic inflammation (Deleidi et al., 2015; Khansari et al., 2009; Leak, 2014; Simpson et al., 2015). In mice, maturation and ageing of the brain affect the density of ionotropic receptors in astrocytes and their function in generation of glial synaptic currents (Lalo et al., 2011). Astrocytes demonstrate age-related changes that resemble senescence, including the SASP: increased level of intermediate glial fibrillary acidic protein and vimentin filaments, increased expression of several cytokines, and increased accumulation of proteotoxic aggregates (Salminen et al., 2011). Moreover, exogenous stresses evoke a typical senescent phenotype in cultured astrocytes, particularly in astrocytes isolated from aged brain. Notably, it was shown that the capacity of several DNA repair pathways in rat neurons and astrocytes decline with age (Swain and Subba Rao, 2011).

In contrast to neurons, which are highly differentiated and postmitotic cells, mature astrocytes retain the ability to proliferate, which means that both the NHEJ and HRR pathways of DSB repair can operate in them. When DSB repair following IR treatment was monitored using γH2AX nuclear foci as a marker of unrepaired DSBs in human embryonic stem cells (hESCs), neural progenitors (NPs), and astrocytes, the rate of DSB repair was higher in NPs and astrocytes compared to hESCs (Adams et al., 2010). However, astrocytes showed less RAD51 foci—an indicator of the HRR pathway—compared to NPs and hESCs. Another study showed surprising reduction in DSB-induced signaling in astrocytes compared to neural stem cells, with DNA-PK rather than ATM being responsible for DSB-induced phosphorylations; however, astrocytes were still proficient for DSB repair, with robust NHEJ (Schneider et al., 2012).

FOXO3a, the main isoform of FOXO transcription factors, mediates the cellular response to oxidative stress by regulating the expression of genes involved in DNA repair and glutamine metabolism, including glutamine synthetase (GS). Immunohistochemical investigation of the population-based neuropathology cohort of the Medical Research Council's Cognitive Function and Ageing Study (MRC CFAS) demonstrates that nuclear retention of FOXO3a significantly correlates with a DNA damage response and with GS expression by astrocytes (Fluteau et al., 2015). Furthermore, GS expression was found to correlate with increasing Alzheimer-type pathology in this ageing cohort. These findings suggest that, in response to oxidative stress, the nuclear retention of FOXO3a in astrocytes upregulates expression of GS as a neuroprotective mechanism (Fluteau et al., 2015). It was also shown that DSB repair capacity is increased in astrocytes induced from a nonreactive into a reactive state (Yong et al., 2014).

Using dissociated cell cultures it was found that Atm-deficient astrocytes show reduced cell arborization (number and length of processes) compared to wild-type (Meshulam et al., 2012). Reduced GFAP staining in *Atm-/-* cerebellar sections indicated reduction in cerebellar valete astrocytes. Similarly, morphological alterations in astrocytes were also found in Atm-deficient retinas and optic nerves, which were associated with reduced retinal functionality as evidenced by electroretinography (Raz-Prag et al., 2011). These findings suggest impaired astrocytic functionality in the Atm-deficient CNS, which may contribute to the neurological phenotype of A-T.

9. Microglia in health, disease and ageing

Microglia are the resident immune cells in the brain. Long viewed as the brain's defenders against biological threats and injury, these chameleon-like cells transform from a resting to an 'activated', macrophage-like state when challenged (Norden and Godbout, 2013). They develop from myeloid progenitors in the yolk sac and migrate to the brain very early in embryonic development (Ginhoux et al., 2010). Thus, they develop alongside neurons during this critical period of brain development and take part in processes associated with building and wiring the developing CNS, ranging from neurogenesis to synaptic pruning. Following injury or disease, microglia are rapidly recruited to sites of damage where they engulf, or phagocytose, debris as well as unwanted and dying cells. Although critical for the immune response to infection or trauma, microglia also contribute to pathological neuroinflammation by releasing cytokines and neurotoxic proteins (Perry et al., 2010; Ransohoff and Cardona, 2010).

Increasing evidence suggests that changes in microglia cells contribute to the age-related deterioration of the CNS. Microglia normally carry out protective roles in response to various immunological stimuli as well as brain injuries (Lull and Block, 2010). In the ageing brain, these stimuli can evoke persistent activation of microglia that results in increased oxidative stress and upregulation of the pro-inflammatory transcription factor, NF-κB (Adler et al., 2008). Thus, 'microglia-ageing' could accelerate brain ageing at large (Block et al., 2007; Conde and Streit, 2006b; Hayashi et al., 2008; Nakanishi and Wu, 2009; von Bernhardi, 2007; von Bernhardi, 2010). Importantly, in the ageing brain, microglia undergo morphological changes: they increase in size and their processes become shorter and thicker, which tags them as "dystrophic microglia" (Conde and Streit, 2006a, 2006b; Flanary et al., 2007; Streit et al., 2004). Ageing microglia undergo a process called 'priming', expressed as enhanced sensitivity to inflammatory stimuli and increased innate immune response. It is unclear whether priming is due to the intrinsic ageing of microglia or is induced by the ageing neural environment. Notably, in a mouse model of premature ageing due to deficiency of the NER enzyme, Ercc1, microglia showed premature priming (Raj et al., 2014), while microglia priming was less prominent in a premature ageing mouse model based on telomere shortening (mTerc$^{-/-}$) (Raj et al., 2015). Consequently, mild stimulations or minor injuries, which are readily resolved in the young brain, may induce damage and cause degenerative changes in the old brain (Herrup, 2010; von Bernhardi, 2007). Separate from the priming phenomenon, microglia from aged brains show increased basal production of IL6 (Sierra et al., 2007; Ye and Johnson, 1999), upregulation of Toll-like receptors (TLRs) and TLR4 co-receptor CD14, and alterations in signal transduction evoked from the activation of TRL4 (Letiembre et al., 2007). Likewise, there are alterations in scavenger receptors of ageing microglia (Hickman et al., 2008; Yamamoto et al., 2002). Aged microglia also express surface antigens that are not normally expressed by young microglia, including the major histocompatibility complex II (MHCII), associated with antigen presentation, and ED1, the rodent equivalent of CD68, associated with phagocytosis. However, the activation of autophagy declines in these cells, resulting in the accumulation of waste within them. Notably, in the *Nbn-Δ*-CNS cerebellum significant reduction in microglial cells was found with normal amounts of astrocytes, suggesting that besides

the severe damage to Purkinje and granule neurons, the absence of Nbs1 also damages the microglia (Galron et al., 2011).

10. In closing

We discussed here the links between DNA damage, genome instability, ageing and degeneration in the brain. The neuronal doctrine that dominated the field of brain research is being replaced by a more holistic view of the brain, with growing recognition of the cardinal role of glial cells in brain structure and function. The term 'glial cells' covers an extremely heterogeneous population of cells whose diverse physiological roles are still being revealed. Thus, the view of the ageing or degenerating brain should take into account this complex cell population. Its importance is just emerging.

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