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DNA damage, neuronal and glial cell death and neurodegeneration

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Abstract The DNA damage response (DDR) is a key factor in the maintenance of genome stability. As such, it is a central axis in sustaining cellular homeostasis in a variety of contexts: development, growth, differentiation, and maintenance of the normal life cycle of the cell. It is now clear that diverse mechanisms encompassing cell cycle regulation, repair pathways, many aspects of cellular metabolism, and cell death are inter-linked and act in concert in response to DNA damage. Defects in the DDR in proliferating cells can lead to cancer, while DDR defects in neurons may result in neurodegeneration. Mature neurons are highly differentiated, post-mitotic cells that cannot be replenished after disease or trauma. Their high metabolic activity generates large amounts of reactive oxygen species with DNA damaging capacity. Moreover, their intense transcriptional activity increases the potential for genomic DNA damage. Respectively, neurons have elaborate mechanisms to defend the integrity of their genome, thus ensuring their longevity and functionality in the face of these threats. Over the course of the past two decades, there has been a substantial increase in our understanding of the role of glial cells in supporting the neuronal cell DDR and longevity. This review article focuses on the potential role of the DDR in the etiology and pathogenesis of neurodegenerative diseases, and in addition, it describes various aspects of glial cell functionality in two genomic instability disorders: ataxia telangiectasia (A-T) and Nijmegen breakage syndrome.

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The DNA damage response (DDR) and the protein systems that govern it

Aberrant response to DNA lesions is implicated in many human neurodegenerative disorders (reviewed in [1, 2]). In healthy cells, the accumulated DNA damage is rapidly detected, leading to activation of an intricate web of signaling pathways known as the DNA damage response (DDR). However, there is evidence for impairment of components of the DDR machinery in some neurodegenerative disorders (reviewed in [2]). Under normal conditions, the DDR may culminate in either activation of cell-cycle checkpoints and appropriate DNA repair pathways, or, in certain contexts, initiation of apoptosis. The DDR is a hierarchical process, executed through a series of steps. The DNA lesions are detected by *sensor proteins* that recognize either the lesions themselves or the subsequent chromatin alterations. *Transducers* are then brought into action, to convey the damage signal to *downstream effectors*. It is this relay system from transducers to effectors, that enables a single DNA lesion to modulate numerous pathways. The transducers may also be involved in the assembly of DNA-repair complexes at the sites of DNA damage (reviewed in [3–6]).

Following the induction of double-strand DNA breaks (DSB), A-T mutated (ATM) is activated, and a portion of nuclear ATM binds to the DSB sites [7]. Part of the activation process of ATM involves autophosphorylation of serine 1981 of the ATM protein, and subsequent

dissociation of inactive ATM dimers into active monomers [8]. While the fraction of ATM that binds to the DSB sites may also be autophosphorylated [9], recent data indicate that this autophosphorylation is not mandatory for ATM recruitment to damage sites [10]. Activation of the ATM kinase seems to be an initiating event in cellular responses to irradiation. ATM may be activated by various types of stress in addition to DSBs [11]. Downstream of the transducer proteins are targets that control various cellular processes such as DNA repair, cell cycle progression, gene transcription, protein synthesis and degradation, and apoptotsis. The Nbs1 protein, which serves as an adaptor protein in the phosphorylation of Chk2, Rad17 and SMC1, is also involved in activation of the intra-S and G2/M checkpoints (reviewed in [6]). The (Breast cancer 1, early onset) BRCA1 C-terminal domain (BRCT) proteins 53BP1 and MDC1/NFBD1, which are recruited to damage-induced foci as sensors, also play roles as mediators and adaptors, and appear to facilitate the phosphorylation of several ATM substrates [12–14]. The Brca1 protein is also a substrate of ATM, and thought to be involved in gene regulation, DNA repair and cell cycle checkpoints [15–18].

Neurons and the DNA damage response

Neurons are unique in being terminally differentiated, post-mitotic cells, while also being extremely metabolically active. Since they are irreplaceable and should survive as long as the organism does, they need elaborate, stringent defense mechanisms to ensure their longevity. Neurons display high rates of transcription and translation, which are associated with high rates of metabolism and mitochondrial activity. The amount of oxygen consumed by the brain, relative to its size, exceeds by far that of other organs. This high activity, coupled with high oxygen consumption, creates a stressful environment for neurons, and noxious metabolic by-products, primarily reactive oxygen species (ROS), are constantly attacking neuronal genomic and mitochondrial DNA [19–25].

The DDR is a major cellular defense system against this threat. It is an elaborate signaling network, activated by DNA damage, involving modulation of many physiological processes [6, 26–28]. Genetic defects in critical relays in this network lead to genomic instability syndromes, which are almost invariably characterized by enhanced sensitivity to specific DNA-damaging agents, chromosomal instability, degeneration of specific tissues including the CNS, and a marked predisposition to cancer [29, 30]. A wealth of information has accumulated on this system in studies on commonly used cancer cell lines [3, 31].

The chromosomal instability syndrome ataxia-telangiectasia (A-T)

The ATM protein was identified as the product of the gene that is mutated in the human genetic disease ataxia-telangiectasia (A-T). A-T is characterized by progressive cerebellar degeneration, immunodeficiency, genome instability, premature aging, gonadal dysgenesis, oculo-cutaneous telangiectasia, extreme radiosensitivity and high incidence of lymphoreticular malignancies (for review, see [32, 33]). One of the most devastating symptoms of A-T, cerebellar ataxia, develops progressively into general neurological dysfunction. One of the main causes of death of A-T patients is aspiration pneumonia, due to swallowing defects related to the cerebellar dysfunction. Post-mortem studies reveal a significant loss of Purkinje and granule neurons in the cerebellum of children with A-T. Clearly, therefore, cerebellar neurons are seriously damaged due to the loss of ATM.

Nijmegen breakage syndrome

Hypomorphic mutations in the NBS1 locus lead to the Nijmegen breakage syndrome (NBS), comprising a combination of microcephaly, mental deficiency, immunodeficiency, radiation sensitivity, chromosomal instability and predisposition to cancer [34–36]. The NBS1 gene product, Nbs1, forms a complex with Mre11 and Rad50 (the MRN complex), which is involved in sensing and processing DSBs and in cell cycle checkpoints [37]. An attempt to elucidate the physiological function of Nbs1 in development failed because of early embryonic death of Nbs1-null mice [38, 39]. A variant of this disease is caused by RAD50 mutation [40].

Hypomorphic mutations in the MRE11 gene lead to another genomic instability disorder: A-T-like disease (A-TLD), which shows marked similarities to A-T. Analysis of three families with affected individuals showed many features of A-T, including the progressive cerebellar degeneration [41, 42]. Although none of the affected individuals exhibited ocular telangiectasia, their clinical presentations were otherwise consistent with the diagnosis of A-T [41]. A-TLD is the only A-T-like disease that does not result from ATM mutations.

The DDR in human aging, and in acute and chronic neurodegenerative pathologies

Compelling evidence points to the central role of cumulative DNA damage in the aging process of CNS neurons and in various neurodegenerative disorders [21–23, 43–48].

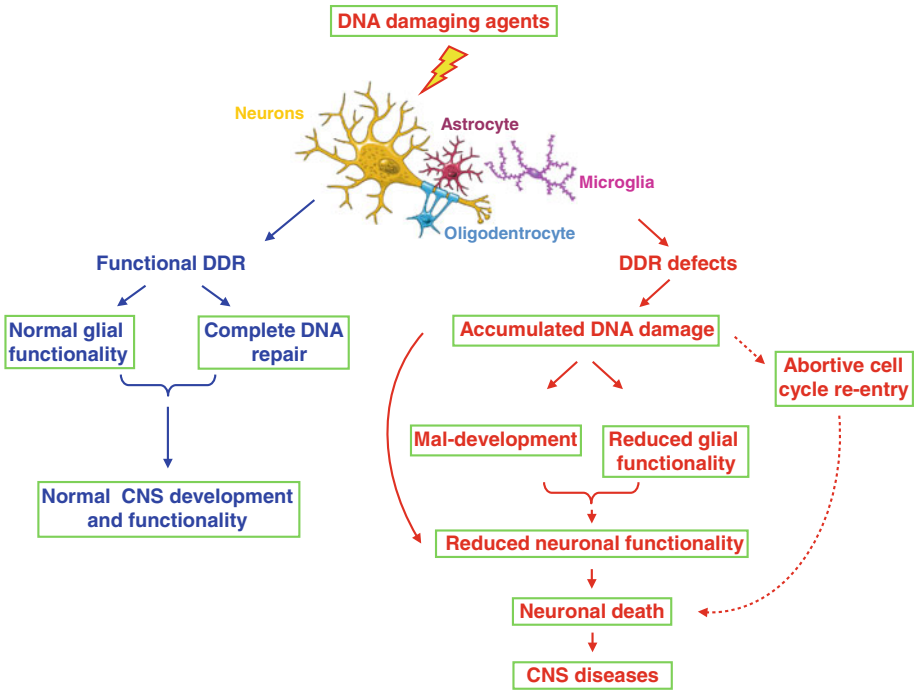

Fig. 1 Effect of defective DDR pathways on the CNS. Accumulation of DNA damage initiates the activation of the DDR machinery. In the healthy brain, the functional DDR leads to normal development and functionality. On the other hand, with early-onset genomic instability disorders, defective DDR machinery leads to cumulative DNA damage, resulting in impaired glial and neuronal development and function. There is evidence, that cumulative DNA damage may trigger postmitotic neurons to undergo abortive cell cycle re-entry, subsequently leading to neuronal cell death. *Dashed arrows* point to processes not yet fully established

However, the aging process does not affect the CNS uniformly [49], and brain regions and types of neurons differ substantially in the amount of the DNA damage that they accumulate during aging [50]. More DNA damage was found in the aging hippocampus than in the aging cerebellum [51]. However, a correlation between DNA damage, DNA repair and neuronal loss in the aging brain is not straightforward: certain types of neurons (such as hippocampal, pyramidal and granule cells as well as cerebellar granule cells) suffer from an age-related accumulation of DNA damage, but are not reduced in number during aging. On the other hand, other types of neurons (such as cerebellar Purkinje cells) are reduced in number during aging, but the remaining cells do not show increased age-related accumulation of DNA damage [48]. It was speculated that there is a certain threshold of cumulative DNA damage, beyond which postmitotic neuronal cells are marked for elimination. Moreover, it has also been suggested, that even before reaching this threshold, the accumulation of damaged DNA within the aging neuronal cell causes substantial impairment in cellular functions [50]. For example, during aging, DNA damage was found to be markedly increased in the promoters of important genes, which manifest reduced expression in the aged brain cortex. Moreover, these gene promoters were also found to be selectively damaged by oxidative stress in cultured human neurons, and show reduced base-excision DNA repair. These DNA damage-related alterations in gene expression have been suggested to play an important role in the pathogenesis of neurodegenerative disorders in the aging brain [52] (Fig. 1).

Potential role of DNA damage and malfunctioning DDR in the pathogenesis of Alzheimer's and Parkinson's diseases

Neurodegenerative disorders can be classified based on many criteria, including age of onset, genetic basis, disease characteristics and clinical course, and affected cell types. Typical late onset, chronic diseases are Alzheimer's disease (AD) and Parkinson's disease (PD), while monogenic disorders such as the genomic instability syndromes are characterized by early onset and acute manifestation. There are common denominators between these two groups of diseases, and accumulation of DNA damage is one of them [21, 23, 48, 50, 53–55]. AD patients are mainly affected in their cerebral cortex however they display progressive neuro-degeneration eventually leading to cognitive decline. Increased oxidative stress and DNA damage were detected in AD patients' neurons [48, 50, 56–59]. Accumulations of DSBs and single-stranded DNA binding proteins (SSBs) as well as activation of the cell cycle program were also observed in certain neurons of AD patients. Interestingly, non-homologous end joining (NHEJ) deficiency and a reduction in the levels of DNA-dependent protein kinase (DNA-PK) (a key element in the NHEJ machinery) were also measured [60–69].

PD is characterized by profound loss of dopaminergic neurons in the substantia nigra pars compacta. A link between ATM deficiency and dopaminergic cell loss was noted by Eilam et al. [70], who showed that ATM-deficient mice exhibited severe degeneration of tyrosine hydroxylase-positive, dopaminergic nigro-striatal neurons, and their terminals in the striatum and the ventral tegmental area. ATM-deficient mice were reported to show locomotor abnormalities, manifested as stride-length asymmetry, which could be corrected by peripheral application of the dopaminergic precursor L-dopa [70]**.** In addition, Atm−/− mice were hypersensitive to the dopamine-releasing drug D-amphetamine. This work also showed that dopaminergic neurons are formed normally in the Atm−/− mice, but degenerate during the first few months of life. The data thus indicate that Atm−/− mice exhibit a progressive, age-dependent reduction in dopaminergic cells of the substantia nigra, followed by a reduction in projection neurons of the striatum. Another common denominator between PD and A-T is elevated oxidative stress and oxidative DNA damage. Elevated labile iron in the substantia nigra pars compacta plays an important role in producing reactive oxygen species (ROS), mainly hydroxyl radicals, which subsequently damage nigro-striatal neurons. Interestingly, the iron chelator desferal increased the radio-resistance of ATM-deficient cells, but did not affect wild-type cells [71], leading the authors to hypothesize that ATM plays a role in cellular resistance to the toxic effects of labile iron. Collectively, these findings may explain the impression that A-T patients show "Parkinsonian" features [72].

Attempts of stressed postmitotic cells neuronal cells to re-enter the cell cycle

Following genotoxic stress, post-mitotic neurons have been extensively documented to attempt to re-enter the cell cycle, an attempt which is abortive, and culminates in apoptotic cell death [69, 73, 74]. Moreover, these cell cycle re-activation attempts has been shown to be a common feature of apoptosis in post-mitotic neurons during development and in neurodegenerative disorders, including A-T [73–79]. Early studies showed that over-expression of the SV40 large T antigen (Tag) in Purkinje and retinal neurons induced DNA synthesis and cell death, but not cell proliferation or tumorigenesis [73, 80, 81]. Targeted disruption of the retinoblastoma protein, pRb, also resulted in DNA synthesis and apoptosis of post-mitotic neurons [73, 82]. The main mechanism of Rb action is considered to be its interaction with and inactivation of the transcription factor E2F. Crossing E2F-1 trangenic mice with Tag transgenic mice resulted in accelerated Tag-induced ataxia and loss of Purkinje cells, suggesting that E2F-1 contributes to the process of degeneration [80]. These mouse models supported the hypothesis that attempts of postmitotic neurons to enter the cell cycle results in neuronal cell death [83]. The fact that neurons are resistant to oncogenic transformation is consistent with this notion [81].

Cell cycle re-activation and neuronal death

It has been suggested, that once cell cycle reactivation is induced by an insult in post-mitotic cells, the extent of the progression of the cell through the cycle is dependent on several factors, including the type of insult, its extent, the type of the neuronal cell and the level of its maturity, all of which collectively act to define a "death threshold" [73, 75, 84, 85]. Kruman et al. [76] have suggested, that these cell cycle re-entry attempts, coupled to cell death following DSB are ATM-dependent. The functional link between neuronal cell cycle re-entry and cell death was demonstrated in many studies. Cell cycling markers have been shown to accompany dopaminergic cell death in the substantia nigra pars compacta in PD. A typical example is high expression of the transcription factor E2F-1 in the affected tissues [86]. Exposure of mice or mesencephalic neuronal cultures to the dopaminergic cell neurotoxins 1-methyl-4-phenyl-1,2,3, 6-tertahydropyridine (MPTP) or 1-methyl-4-phenylpyridinium ion (MPP^+) resulted in the activation of the retinoblastoma-E2F pathway in post-mitotic neurons prior to their subsequent death. Remarkably, E2F-1 deficient mice were significantly more resistant to MPTP-induced dopaminergic cell death than their wild type littermates. Exposure of cerebellar granule neurons to MPP^+ resulted in increased expression of cyclin D, cyclin E, CDK2, CDK4 and E2F-1. Broad inhibition of cyclin dependent kinases (CDKs) attenuated the neurotoxic effects of MPP^+ [87]. hawse have shown that exposure of chick sympathetic neurons to dopamine resulted in apoptotic cell death which was associated with fluctuation in the expression of cyclin B2 and PCNA [88, 89]. Similar to cerebellar granule neurons, which are sensitive to dopaminergic neurotoxins, Purkinje cells were also found to be vulnerable to a variety of insults during development and maturity. Apoptotic death in Purkinje cells has been shown to be associated with markers of active cell cycle and new DNA synthesis in the *staggerer* and *lurcher* mutant mice (These mice are characterized by intrinsic Purkinje cell deficiencies and, in both mutants, substantial numbers of cerebellar granule cells and inferior olive neurons die due to the absence of trophic support from their main postsynaptic target.) [90]. In rat cerebellar organotypic cultures, CDK inhibitors extended the life of Purkinje neurons, but their morphology appeared abnormal [91]. CDK involvement has also been found in cell death induced by cerebral ischemia [92]. In patients with spinal cord injury, up-regulation of cell cycle genes was associated

with neuronal and oligodendrocyte apoptosis, and treatment with the cell cycle inhibitor flavopiridol was shown to reduce cell cycle protein levels and to significantly improve functional recovery [93, 94].

In order to enter the cell cycle, quiescent postmitotic neurons must exit G0 and enter into the G1 phase. Several studies reported expression of G1/S cell cycle regulators in neurodegenerative diseases such as AD [65, 95, 96], vascular dementia [96], amyotrophic lateral sclerosis (ALS) [97], and also in spinal cord injury [98], hypoxia–ischemia [99], and cultured primary neurons undergoing cell death [100]. Moreover, G1/S cell cycle blockers, inhibitors of CDKs and expression of mutant, dominant-negative CDK4/6 have been shown to promote the survival of neurons following DNA damage and growth factor withdrawal [77–79, 101, 102]. Cyclin D1 has been reported as an essential mediator of neuronal apoptotic death which is p53-independent, with respective Cdk activation [73, 103], exemplifying a link between the cell cycle machinery and neuronal cell death. Phosphorylation of pRb and activation of E2F in neurons following an apoptotic stimulus, including DNA damage, have also been documented [73, 74, 78, 100]. The mechanism by which CDKs are activated in stressed neurons remains elusive. It was recently suggested that checkpoint kinase 1 (Chk1) is a potential activator of the cell cycle in neuronal death induced by DNA damage. In cortical neurons under non-stressed conditions, the basal activity level of Chk1 is relatively high and has been suggested to contribute to the post-mitotic state of neurons. It was reported that in neurons, Chk1 activity is rapidly down-regulated following DNA damage, with a concomitant increase in Cdc25A activity. In proliferating cells, Cdc25A phosphatase dephosphorylates and activates CDK4/6/cyclin D1 complex. Following DNA damage, it is negatively regulated by phosphorylation, a process mediated, among others by Chk1. In neurons, inhibition of Cdc25A blocks neuronal death and reduces cyclin D1-associated kinase activity and pRb phosphorylation. Therefore, it has been suggested that the Chk1/Cdc25A axis participates in the activation of cell cycle-mediated neuronal death [104]. Another important mediator of the G1/S cell cycle checkpoint is p53. Cerebellar granule neurons deficient in p53 are more resistant to apoptosis induced by DNA strand breaks [73]. In postmitotic neurons, similar to proliferating cells, the transcription factors E2F and p53 induce expression of genes that function in death pathways [73, 105].

Re-activation of the cell cycle in stressed postmitotic neurons and the S-phase

The question whether postmitotic neurons re-entering the cell cycle go through DNA synthesis before succumbing to the apoptotic process is still debated. Expression of S-phase markers was reported in post-mitotic neurons following DNA damage [76], hypoxia–ischemia [99], and in neurons ectopically expressing E2F1 [106]. Moreover, DNA synthesis was documented in neurons in AD [107], and lately in A-T [108]. FACS analysis showed an increase in S-phase cells among neurons exposed to genotoxic insults [76]. Interestingly, ATM suppression was found to attenuate the damage-induced S-phase re-entry and consequently the apoptotic process in damaged neurons [76]. These findings are in line with earlier findings of resistance of neuronal tissues in Atm−/− mice to DNA damage-induced apoptosis [109–111].

The potential of stressed neuronal cells to pass the G1/S phase checkpoint and synthesize DNA before triggering of apoptosis might be linked to their survival span after the initial injury [99]. The "death threshold" mentioned above is important in determining the involvement of cell cycle signaling in neuronal death [85]. It has been suggested that DNA synthesis itself is a potential source of replication errors. Since differentiated neurons predominantly express DNA polymerase β with a high error rate, de novo synthesis following neuronal cell cycle re-entry might produce additional DNA damage that eventually leads to cell death [85]. A mouse model of oxidative stress-mediated neuro-degeneration demonstrated a direct connection between oxidative stress, cell cycle re-entry, DNA synthesis and apoptosis [112]. Apoptosis-inducing factor (AIF)-deficient harlequin (Hq) mice undergo neurodegeneration associated with a 40–50% reduction in complex I level and activity, and show progressive ataxia in aged mice [112]. *Hq* cerebellar granule cells exhibit oxidative stress, DNA damage, abortive S phase progression and expression of caspase 3. This mouse provides in vivo evidence that oxidative stress and DNA damage in post-mitotic neurons are associated with cell cycle re-entry extending to the stage of DNA synthesis.

Re-activation of the cell cycle in stressed postmitotic neurons and the G2-phase

Expression of G2/M checkpoint markers has been reported in A-T cells [108], AD [95, 107], vascular dementia [96] and several other neurodegenerative diseases [113]. CDK1 has been shown to phosphorylate the pro-apoptotic protein BAD in neurons, thus providing another evidence for the link between the cell cycle and the cell death machinery [73, 114]. It has also been suggested that activation of CDK1 in neurons leads to hyper-phosphorylation of other proteins such as cyclin B1 and cdc2 implicated in the pathology of neurodegenerative diseases [113, 115].

Despite the data on neuronal cell cycle re-entry through G1/S, DNA synthesis and G2, there is no evidence for entry

of neurons into the M phase [65, 73, 107]. Postmitotic neurons have not been shown the have ability to undergo chromosome segregation and cytokinesis [73]. The reasons why there is, on the one hand, expression of cell cycle proteins in stressed postmitotic neurons, while, on the other hand, these cells fail to follow routine cell cycle progression including cell division [95] remain to be elucidated. The co-expression in the stressed potmitotic neuron of cell cycle proteins that normally function at different stages of the cell cycle argues for de-synchronization of the cell cycle stages as one of these reasons [65, 95]. In addition, inhibitory proteins associated with cell cycle exit, such as members of the INK4 family of CDKIs, have been shown to be up-regulated in vulnerable AD neurons [95, 116, 117]. Moreover, many of the cell cycle proteins are often found in the cytoplasm of the neurons and not in the nucleus where they normally exert their cell cycle-related activities [65, 73, 95, 97, 105, 113]. This altered localization further led to the notion, that cell cycle proteins may have additional functions, other than cell cycle progression, that may contribute to the cell death process [73, 105]. Another interesting perspective, relates to the fact that the mitochondrial mass, with its concomitant potential to generate oxygen radicals is highest just before the M phase, thus potentially increasing oxidative threat and adding further damage to the DNA, that ultimately leads to cell death and not mitosis [96].

A different view on the observed of cell cycle re-entry in damaged neurons suggests the relation between this phenomenon and cellular survival pathways. In cycling cells, cell cycle progression following DNA damage is arrested at specific checkpoints to allow time for damage assessment and processing. Therefore, it is possible that the cell cycle re-entry of damaged neurons may be required for activation of the repair process. It is noteworthy that various repair enzymes have greater activity in proliferating cells than in post-mitotic neurons and some of the DNA repair processes are completely attenuated in neurons, as mentioned above. Since lesions are repaired more slowly in neurons than in dividing cells [118–120], the triggering of cell cycle re-entry following DNA damage might lead to activation of the DNA repair process by mimicking the cycling state [74]. Transient expression of components of the homologous recombination (HR) repair pathway was reported following apoptotic stimuli, and was correlated with increased DNA repair [121]. Expression of the base excision repair enzyme Ref-1 was significantly increased in AD compared to controls [61]. DNA-polymerase β, which functions in DNA repair [122–124], is loaded into replication forks in neurons challenged with β amyloid [125]. GADD45a and GADD34 (members of the growth arrest and DNA damage gene family), which are also known to mediate DNA repair together with PCNA, were found to be expressed in post-mitotic neurons following spinal cord injury and focal cerebral ischemia, together with other cell cycle-related genes [98, 126]. Thus, it might be that activation of the cell cycle in post-mitotic neurons is intended to activate efficient rapid repair machinery, similar to that operative in proliferating cells. Conceivably, there may be a threshold of DNA damage, beyond which, the pathways to DNA repair in the neuronal cells are overwhelmed, thus leading to the initiation of the cell death signaling cascade [121, 127]. Reduced expression of DNA repair proteins, as suggested in neurodegenerative diseases [60–62] is compatible with this view [61]. Taken together, all these lines of evidence indicate important roles for cell cycle re-activation and DNA repair systems in the DDR, which when failed, culminates in initiation of the apoptotic process.

Glial cell fate in mouse models of A-T and NBS

Following the neural doctrine of neurodegenerative diseases, most of the studies regarding cerebellar degeneration in A-T patients and Atm-deficient mice focused on the effects of Atm-deficiency on the fate of Purkinje and granule neurons. In contrast, very few studies focused on the role of glial cells in the etiology of A-T. Among these studies, Glial cell abnormalities were detected in post mortem study of brain tissue from a 32-year-old A-T patient, where multiple small glio-vascular malformations in the brain and spinal cord were found [128]. Using electron microscopy, Kuljis et al., found glial activation in Atm deficiency models associated with the degeneration of cerebellar neuronal cells [129]. Furthermore, Atm deficiency retarded the growth of cultured primary astrocytes and caused early senescence, as well as an increased rate of glial cell death. Atm−/− astrocytes showed markers of oxidative and ER stresses, including increased levels of heat shock proteins, SOD1 and elevated phosphorylation of ERK1/2, which was seen primarily in cerebellar astrocytes or Bergmann glia [130]. Bergmann glia are cerebellar astroglial cells that have their soma in the Purkinje cell layer and extend fibers across the molecular layer to the pial membrane. Their processes wrap somata, dendrites, and dendritic spines of the Purkinje cells and their excitatory and inhibitory synapses.

To further analyze the mechanism by which Atm deficiency slowed down cell growth, and initiate early senescence and cell death, Kim and Wong studied the effect of Atm inactivation on the astrocytes redox state. They found that intrinsic elevated intracellular concentrations of ROS were associated with senescence-like growth defects of Atm−/− astrocytes. These results suggest that Atm is required for normal astrocytic growth, through its ability to stabilize the intracellular redox status [131]. Cultured cells

from A-T individuals or Atm−/− mice have observed to have cell cycle perturbations, as well as growth defects, and are generally considered radiosensitive. However, it has been shown that certain cell populations in the Atm−/− central nervous system are radio-resistant. These results demonstrate that CNS neural and glial populations are more radio-resistant compared to non-CNS proliferating cells. To further define specific ionizing radiation (IR) sensitivities of cell populations within the CNS, Gosink et al. analyzed Atm−/− astrocytes, and found that Atm−/− astrocytes exhibit premature senescence, express constitutively high levels of p21 and have impaired p53 stabilization. However, in contrast to radiosensitive Atm−/− fibroblasts and radio-resistant Atm−/− neurons, survival of Atm−/− astrocytes after IR was similar to that of wild-type astrocytes. Additionally, p53-null astrocytes but not fibroblasts were moderately more radio-resistant than their wild-type counterparts, suggesting that the deficit in p53 stabilization observed in Atm-null cells is not a measure of radiation susceptibility. These data suggest, that in astrocytes, the functions of Atm in cellular growth and radiosensitivity are distinct [132].

In the context of the Nijmegen breakage syndrome (NBS), Nbs1 is a component of the Mre11/Rad50/Nbs1 (MRN) complex that acts as a sensor of double strand breaks (DSBs) in the DNA and which is critical for proper activation of the broad cellular response to DSBs. Conditional disruption of the murine ortholog of the human NBS1, Nbs1, in the CNS of mice was previously reported to cause microcephaly, severe cerebellar atrophy and ataxia. Interestingly, morphological and biochemical analyses of the Nbs1-CNS-Δ revealed a profound effect on the integrity and the functionality of the glial cells, which suggests their crucial role in the pathogenesis of NBS. Using conventional T2-weighted magnetic resonance (MRI), we found that the brains of the mutant mice (Nbs1-CNS-Δ) were significantly smaller than those of the wild-type animals, with marked mal-development of the cerebellum. Region of interest analysis of the T2 maps revealed significant T2 increase in the areas of white matter (corpus callosum, internal capsule and midbrain), with minor changes, if any, in gray matter. Diffusion tensor imaging (DTI) data confirmed that fractional anisotropy values were significantly reduced in these areas, mainly due to increased radial diffusivity (water diffusion perpendicular to neuronal fibers). Biochemical analysis showed low and dispersed staining for myelin basic protein (MBP) and galactosylceramide (GalC) in Nbs1-CNS-del brains, indicating defects in myelin formation and oligodendrocyte development. Myelin index and myelin protein levels were significantly reduced in these brains, indicting a widespread glial damage, and a novel function of Nbs1 in the development and organization of the white matter [133].

Galron et al. have found direct evidence that malfunctioning DDR can diminish glial cell functionality and thereby play a key role in the etiology of NBS in the mouse model of this disease (unpublished data). In this study, it was shown that conditional inactivation of the murine *NBS1* gene has a profound effect on the integrity and the functionality of glial cells, suggesting their crucial role in the pathogenesis of NBS. Malfunctioning DDR significantly attenuated the secretion of astrocytes and microglia-derived growth factors. Whereas the levels of the *NBS1* gene were markedly reduced in astrocytes, no change in the levels of the *NBS1* gene was detected in microglia. Additionally, while no alterations in the number of Purkinje cells were found in mice in which the *NBS1* gene was specifically deleted in Purkinje cells (Nbs1-PC-Δ) compared to WT mice, there was a significant reduction in the number of Purkinje cells in the Nbs1-CNS-Δ mice. Furthermore, a significantly reduced performance in the rotarod test was observed in the Nbs1-CNS-Δ mice in this study (Rotarod is used to assess motor coordination of mice and rats. The animals are placed on textured drums to avoid slipping. When an animal drops onto the individual sensing platforms below, test results are recorded).

These results suggest that Nbs1-deleted Purkinje cells can thrive in an environment in which the glial cells are fully functional. These results further suggest that malfunctioning astrocytes in Nbs1-CNS-Δ mice generate stress conditions, cannot properly recruit microglia cells to stressed regions in the mouse brain, and cannot provide proper support to neuronal cells. This study emphasizes the importance of the environment in which the cerebellar cells function and the respective support provided by the glial cells. In general, it strengthens the notion that the pathogenesis of neurodegenerative disorders is not dependent on a defect in certain type of cells, i.e., solely neuronal cells or certain types of glial cells, but rather from an integrative malfunction of the neuronal-glial environment.

Conclusions

The DNA damage response is a key factor in the maintenance of genome stability. As such, it is a central axis in sustaining cellular homeostasis in a variety of situations: development, growth, differentiation, and maintenance of the normal life cycle of the cell. It is now clear that diverse mechanisms encompassing cell cycle regulation, repair pathways, many aspects of cellular metabolism, and cell death are inter-linked and act in concert in response to DNA damage. Defects in the DNA damage response in proliferating cells can lead to cancer while defects in neurons result in neurodegenerative pathologies. DSBs are one of the most cytotoxic forms of DNA damage.

Respectively, the cellular response to DSB is a multi-tiered process that begins with rapid recruitment to the break sites of early damage response sensor proteins, such as the Mre11-Rad50-Nbs1 (MRN) complex. These proteins participate in initial processing of the damage and gradually build up a signaling cascade that leads to the activation of the transducers. The primary transducer of the DSB alarm is the nuclear serine/threonine kinase ATM. ATM and other transducer proteins convey the message by the phosphorylation of hundreds of effector proteins which activate global cellular responses. Inactivation or mutations in key components of the DDR machinery can lead to generation of syndromes such as A-T or NBS. These are related genomic instability syndromes caused by null alleles in the *ATM* gene or hypomorphic mutations in the *Nbs1* gene. Mounting evidence supports the notion that mal-functioning DDR plays an important role in the etiology of late onset neurodegenerative syndromes such as Alzheime's and Parkinson's disease. Interestingly, surprising similarities can be drawn between the early onset syndrome A-T and the late onset Parkinson's disease. In both these diseases, mal-functioning DDR is observed. The brain is composed of unique cell populations of neurons and glia. Neurons, perhaps more than any other cell type, are characterized by an elaborate structure and function. The combination of their critical function, post-mitotic nature, finite number and high metabolism demands a well-defined support environment to optimize their functionality. Glia, which are proliferative cells, are unique in terms of their ability to form connections with many other cells and are critically important for the generation of the homeostatic environment neurons require to function properly. Moreover, glial cells and especially astrocytes are third parties to all synapses in the nervous system. Each astrocyte can modulate up to 15,000 synapses. Moreover, glial cells control the level of neurotransmitters, secrete their own transmitters and participate in the processing of signal transmission. It is crucial to elucidate the interrelations between neurons and glia,—especially the role of each cell type in the etiology of neurodegenerative diseases. Until recently, neurons attracted most of the attention as the main player in neurodegenerative disease etiology. However, emerging evidence supports the notion that glial cells are critically important for brain development and functionality. In this review article we present evidence that supports the notion of a glial doctrine, whereby glial cell malfunction is portrayed as a major causal element of neurodegenerative disease. This notion is likely to be revisited and further investigated. In conclusion, what is clearly needed is a better understanding of the DDR complex machinery. Identifying junction points in this intricate web of cellular interactions and responses will enable us to interfere so as to devise novel therapeutic regiments. Especially in brain diseases, clarification of the relative contribution of glial cells as well as neurons to the etiology of neurodegenerative disease will help guide the search for novel treatment modalities for a variety of neurodegenerative conditions. Glial cells make up the largest cell population in the brain and are continuously renewed over the course of a human's lifetime, which makes them an attractive target for therapeutic intervention in neurodegenerative disorders. Hence, modifying the activity of glial cells to enhance their neuroprotective features such as the secretion of specific neruotrophic factors or alternatively modulation of neurotransmitter release may hold promise as new directions in the search for therapeutic interventions in genomic instability as well as late onset neurodegenerative disorders.

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