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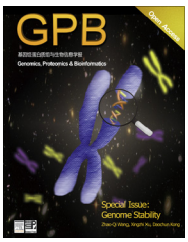

REVIEW

Connecting Malfunctioning Glial Cells and Brain Degenerative Disorders

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Abstract The **DNA damage response** (DDR) is a complex biological system activated by different types of DNA damage. Mutations in certain components of the DDR machinery can lead to **genomic instability** disorders that culminate in tissue degeneration, premature aging, and various types of cancers. Intriguingly, malfunctioning DDR plays a role in the etiology of late onset brain degenerative disorders such as Parkinson's, Alzheimer's, and Huntington's diseases. For many years, brain degenerative disorders were thought to result from aberrant neural death. Here we discuss the evidence that supports our novel hypothesis that **brain degenerative diseases** involve dysfunction of **glial cells** (**astrocytes**, **microglia**, and oligodendrocytes). Impairment in the functionality of **glial cells** results in pathological neuro-glial interactions that, in turn, generate a "hostile" environment that impairs the functionality of neuronal cells. These events can lead to systematic neural demise on a scale that appears to be proportional to the severity of the neurological deficit.

The DNA damage response

The most serious threat to genome stability is damage inflicted on DNA molecules [1]. Although DNA damage is usually mentioned in connection with environmental agents, in fact most of the ongoing damage to the cellular genome – estimated around tens of thousands of lesions each day – is caused by endogenous reactive oxygen species (ROS) produced during normal metabolism [1,2]. Proper action of the defense systems that guard the genome against these ongoing threats is critically important for cellular homeostasis and development, as well as prevention of undue cell loss, premature aging, and various types of malignancies [3,4]. These defense systems respond to DNA lesions by activating specific DNA repair mechanisms, which operate on a variety of DNA base lesions, base-pair mismatches, crosslinks, as well as single-strand breaks (SSBs) and double-strand breaks (DSBs) [5]. DNA repair is, however, just one arm of the broad DNA damage response (DDR). The DDR is an elaborate signaling network that swiftly modulates many physiological processes; it constitutes one of the most comprehensive cellular responses to

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physiological stimuli [6]. Recognition of the breadth and power of the DDR has come mainly from studies of the response to the DNA DSB – an extremely cytotoxic DNA lesion that vigorously activates the DDR [7].

The relationship between genome stability and human health is highlighted by the genome instability syndromes. Patients with these syndromes are typically characterized by progressive degeneration of specific tissues, chromosomal instability, cancer predisposition, and increased sensitivity to DNA damaging agents [8–10]. Predisposition to specific types of cancers can be conferred by heterozygosity for mutations that inactivate certain DDR components, such as p53, breast cancer type 1 susceptibility protein (BRCA1), breast cancer type 2 susceptibility protein (BRCA2), and mismatch repair (MMR) proteins [11–13]. These phenotypes highlight the intimate link between genome instability and the formation and progression of cancers [4,14]. It has recently become evident that variations in DDR efficiency contribute to the development of metabolic and cardiovascular diseases [15,16]. It is our notion that combinations of sequence alterations in DDR genes account for a continuum of variation in genome stability in the human population that affects public health on a large scale.

Mutations in key DDR molecules are implicated in human genomic instability syndromes [17]. These disorders include ataxia-telangiectasia (A-T, mutation in the *ATM* gene encoding ataxia-telangiectasia mutated) [18], ataxia-telangiectasia-like disorder (A-TLD, mutation in meiotic recombinant 11 homolog; *MRE11*) [19], Seckel syndrome (mutation in ataxia telangiectasia and Rad3 related; *ATR*) [20], and Nijmegen breakage syndrome (NBS, mutation in nibrin *NBS1*) [21]. Patients suffering from A-T, A-TLD, or NBS exhibits symptoms involving neural and lymphoid organs. A-TLD patients generally have a slower progression of disease than A-T patients do [22,23]. NBS patients have a phenotype on the cellular level similar to A-T, except that cerebellar defects are different [21,24–27]. The phenotype of the Seckel syndrome overlaps with some features of A-T, A-TLD, and NBS (*e.g.*, microcephaly, mental retardation, genomic instability, and hematological malignancies). Patients with each of these diseases have neurological defects, suggesting that the DDR is important in neurogenesis and neurodegeneration.

A-T – a brain degenerative disease caused by genome instability

Malfunctioning DDR is implicated in many human brain degenerative diseases (BDDs) [28] including the prototypical genome instability syndrome A-T. The hallmarks of A-T are severe neuro-motor dysfunction (emanating primarily from progressive cerebellar atrophy), telangiectasia (formation of small dilated blood vessels), immunodeficiency, sterility, a striking predisposition to lymphoid malignancies, extreme sensitivity to ionizing radiation, and, in some patients, growth retardation, premature aging, as well as insulin-resistant diabetes [29–31]. Cerebellar ataxia is one of the most devastating symptoms of A-T and progressively develops into general motor dysfunction [32]. One of the main causes of death of A-T patients is aspiration due to cerebellar-related swallowing defects [33]. Post-mortem studies reveal a significant loss of Purkinje and granule neurons in the cerebellums of young A-T patients, and therefore this disease was once considered a "Purkinje cell disease" [34,35]. The observed damage to cerebellar neurons due to the loss of the *ATM* gene supports the "neuron doctrine" thought to underlie neurodegenerative diseases. Cellularly, A-T is characterized by cerebellar degeneration of various cell types, premature senescence of fibroblasts, chromosomal instability, and hypersensitivity to DNA-damaging agents, particularly those that induce DSBs [36]. Such increased sensitivity results from a profound defect in the cellular response to DSBs, which in normal cells chiefly mobilize ATM kinase [8].

Malfunctioning DDR affects brain functionality

ATM deficiency is a representative of genomic instability disorders that severely affect brain functionality. Thus, we will focus on ATM deficiency and its effects on neuronal and glial cell functionality. Neurons contain significant levels of ATM in the cytoplasm [37]. The cytoplasmic ATM is found in synaptosomes, the synaptic termini of neurons, where it forms a complex with synaptobrevin (also known as vesicle-associated membrane protein 2, VAMP2) and synapsin-I. Synaptobrevin is part of a complex structure know as soluble *N*-ethylmaleimide-sensitive factor activating protein receptor (SNARE) that mediates synaptic vesicle fusion with the cell membrane during the release of neurotransmitters, while synapsin-I is an abundant neuronal phosphoprotein that is associated with synaptic vesicles [38]. Interestingly, both synaptobrevin and synapsin-I must be phosphorylated in order to bind ATM [37]. ATM deficiency leads to reduced long-term potentiation (LTP) at the Schaffer collateral-CA1 pathway, suggesting a role for cytoplasmic ATM [37].

It is highly likely that information coding in the brain is not performed at the level of single neurons but rather at the level of neural-glial networks [39]. Many BDDs are characterized by malfunctioning DDR, and it is important to understand how malfunctioning DDR influences the dynamics of neural-glial networks. Using microelectrode arrays to simultaneously record data from many neurons, Levine-Small et al. [40] analyzed how ATM deficiency affected the dynamics of neural-glial networks. Interestingly, no differences in firing activity between individual wild-type and ATM-deficient neurons were detected in response to DNA damage. In contrast, ATM deficiency led to a decrease in synchronization persistence compared to wild-type cortical networks following chemically-imposed DNA damage. These findings support the notion that neurological symptoms are not always the product of the malfunction of one cell but rather result from the failure of interacting networks. Thus, an additional implication of the study by Levine-Small et al. is that understanding the systems-level network is critically important for general comprehension of BDDs and for the development of treatment modalities for brain illness.

In a quest to understand the role of ATM in the activity of Purkinje cells, Chiesa et al. conducted morphological and electrophysiological analyses of Purkinje cells from $ATM^{-/-}$ mice of different ages [41]. No histological or immunohistochemical abnormalities were found in these mice. Electrophysiological analyses revealed no abnormalities in resting membrane potential, input resistance, or anomalous rectification. However, significant reductions in the durations of calcium and sodium