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The molecular crosstalk: oxidative stress, genomic instability and neurodegenerative disorders.

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Abstract

Genomic stability is a commitment of regulation and establishment of cell lines in organisms. The instability of genomes greatly affects maintenance of genetic profile and is directly or indirectly associated with many disorders. With the exception of cancer, genomic instability is widely associated with neurodegenerative disorders. The conflicts among the molecular mechanisms, such as replication, transcription, and translation are majorly responsible for the genomic instability, among which, transcription-replication conflict is well understood. Despite immense research on DNA damage and repair systems, Reactive oxygen species and impaired disorders; neurodegenerative disorders are one of the prime causes for the high-level mortality. This article focuses on the replication-transcription conflicts, genetic basis of neurodegenerative disorders and possible medical applications and may help in understanding the molecular mechanisms and finding new biomarkers and therapeutic developments.

Keywords: Reactive oxygen species, Neurodegenerative disorders, Biomarkers, Oxidative stress.

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Introduction

The genomes of all organisms are frequently modified by either endogenous factors produced *via* respiration process or by exogenous factors that include physical, chemical and biological agents, therapeutics agents etc. These factors promote the genome instability and subsequently lead to lethal diseases such as cancer, neurological diseases, immunodeficiency's etc. [1]. Therefore, cells need an effective mechanism that could protect the DNA from endogenous and exogenous stress. DNA damage response pathway, which is specialized machinery, helps in repairing the errors that occur during transcription and translation processes [2]. According to the recent studies, parasites are the major causative agents for cancer and it is estimated that about 18% caused by virus, bacteria, fungi and other parasites such as *Helminthes*. In general, parasitic infection activates the immune response and leads to inflammatory disorders. Chronic inflammation procedures produce free radicals such as Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) that lead to cancer and associated genomic instability [3].

The Replication-Transcription Conflict

DNA replication and transcription are essential processes that help in cell growth and division. There is a conflict between these processes, which cause the genome instability as the polymerases get charged in both the processes and share the common template. Among all fast growing conditions, such as replication, transcription, repair and recombination, chances are very high for simultaneous increment in this molecular process conflict. DNA replication and transcription is one of the best studied molecular mechanisms with regard to this issue. There are two kinds of collisions, named as head-on collision and co-directional collision, are associated with this event. In head-on collision, replicative helicase and RNA polymerase, translocated along the lagging strand in opposite direction, whereas, in co-directional collision, the translocation takes place in leading strand in the same direction [4]. Paul et al. found higher level of point mutations in the core genes of lagging strand compared to the leading strand. The study concluded that head-on conflict is more mutagenic than co-directional collision conflict. Therefore, most of the organisms promote faster evolution of specific genes *via* orientation-dependent encounters between DNA replication and transcription [5]. DNA Polymerases (Pols) have extensive role in DNA damage repair and maintain the genome integrity. Recent studies have reported that unscheduled activation of Pols lead to the genomic instability by altering the genomics regions. For this reason, these Polymerases responsible for specific repairing should be strictly regulated. It is believed that only 4 polymerases named α, β, ξ and γ are essential for stability of DNA, but more than a dozen are required to stabilize the mammalian DNA. Out of the four, potential roles of Poly β and γ are well explained. Poly β is essential in base excision repair during development of brain, whereas Poly γ is not essential but altered levels may cause various types of DNA damage [6]. The head-on encounter between RNA and DNA polymerases affects the genomic integrity. Therefore, signal transduction pathways like stress activated protein kinases play a key role in gene regulation in environmental

stress. In a recent study, Duch et al. reported the role of *Hog1* and *p38* in Yeast and mammalian, respectively. Furthermore, the study stated that *Hog1* delaying the replication prevent the conflict between RNA and DNA polymerases [7].

Replication and transcription conflict causes the high-level damage in chromosome duplication and gene expression. Now, there is an increased interest in understanding the mechanisms of transcription-replication interferences, often which are beneficial to the cell. Numerous processes have been evolved to avoid or resolve the problems which occur due to replication and transcription conflict. However, further investigations are needed to find out the epigenetic markers that influence the genome integrity [8,9]. Recent studies reported few proteins that answer several questions in relation to the conflict between replication and transcription. Duch et al. reported *Hog1* and *Mrc1* acts as "S" phase check point that prevent the eukaryotic replication and transcription conflict, otherwise it would lead to the genomic instability [10]. A recent study demonstrated that transcription factor-operator complexes could halt the DNA replication and DNA recombination enzymes are essential to activate the blocks [11]. Replication process is faster than that of transcription; therefore, frequent collisions between replisome and RNA polymerase (RNAP) may occur. RNAP backtracking may evoke problem in nucleotide arrangement in the DNA and hamper the genome stability; therefore, there is a need of multiple transcription elongation and termination factors that could effectively decrease the backtracking process by which the genome is stabilized. In their study, Dutta et al. concluded that the structural organization of replisome and RNAP are highly preserved in the process of evolution. Therefore, the similar mechanism (Transcription driven genomic instability) they reported in *E. coli* may be applicable for the higher organisms too [12]. Replication proteins also play critical multiple roles in cells, particularly, in DNA replication check point activation. However, there are still questions remain that how the replisome proteins activate the checkpoints and maintain the fork stability [13].

Molecular pathways that minimize the conflict between replication and transcription are well studied and characterized in prokaryotic cells, but over the years, it remains as an important question for eukaryotic cells. A recent pathological study reported R-loop formation, which is an outcome of replication and transcription conflict. The uncontrolled conflict between replication and transcription and unscheduled R-loop accumulation lead to the genomic DNA instability and neurodegenerative diseases. There is a need to unfold the molecular mechanisms that could reduce the transcription induced replication stress, therefore, a framework for understanding the molecular basis of cancer could be developed [14]. "All cells have evolved important auxiliary replication restart proteins and an array of recombination-mediated mechanisms to safely negotiate a variety of conflicts in order to complete accurate genome duplication. Recombination-mediated restart mechanisms are inherently more precarious if not coordinated tightly, while direct restart mechanisms are safer in maintaining genomic stability" [15].

Oxidative Stress and DDR in Neurodegenerative Disorders

Oxidative stress and reactive oxygen species

Oxidative stress or reactive oxygen species are responsible for many health impairments. Reactive oxygen species and impaired antioxidant defense cause the chronic renal failure [16]. Furthermore, antioxidant vitamins serves as a method of preventing complication related to the renal failure [17] and simvastatin can prevent dimethylnitrosamine-induced oxidative stress in kidney [18]. It is well-known that physical exercise increases the production of free radical generation. In a study, Guo and Qi reported that polysaccharide from Cortex Eucommiae (A Chinese herbal medicine) has protective effect on exercise induced oxidative stress by increasing the antioxidant enzymes in blood, liver and muscle [19].

Oxidative stress markers show highly increased levels during the infections than non-infected or controls. In a study, Dkhil et al. reported that intestinal response to *P. chabaudi* infection might help in understanding the process of intestinal oxidative stress and the gene regulation by mucin. However, the molecular mechanisms are not yet clearly understood [20]. Oxidative stress is one of the causes for the heart failure other than the regular myocardial infarction, hypertension, cardiomyopathy and valvular heart disease. It is important to determine the role of antioxidants in the heart failure and identification of biomarkers. Eren et al. studied the association of HDL-associated PON1 activity in heart failure. The study aimed to correlate HDL-associated antioxidant enzymes, Paraoxonase (PON1) and Arylesterase (ARE). Total Oxidative (TOS) and Antioxidative Status (TAS), in Heart Failure (HF) patients concluded that the NYHA (New York Heart Association) classes of heart failure promotes free radical generation apart from uric acid synthesis. The study further suggested that during the worst heart failure the oxidative stress enhances [21]. Moreover, studies reported that oxidative stress is associated with oxidative DNA damage in lymphocytes [22], may cause emotional stress which further leads to impairment in lymphocytes a possible comorbidity of anxiety and acne [23]. Razavipour et al. reported the role of nickel nanoparticles in increasing the oxidative stress of immune system. The study concluded that nickel oxide nanoparticles could effectively release the free radicals and destroy the tissues of immune system [24].

Oxidative stress contributes in dopamine cell degeneration in Parkinson's disease (PD). However, imbalance between free radicals and antioxidants play crucial role in pathogenesis of Parkinson's disease. Nikam et al. reported that the elevated levels of free radicals cause the loss of neurons and lead to PD. On the other hand, the decreased levels of antioxidants are indirectly responsible for neural loss by decreasing their self-activity [25]. Evidences suggested that brain is the most potential route of absorption for environmental hazardous elements, such as electromagnetic radiation. Malondialdehyde protects the brain from radiation and serves as a biomarker for neural tissue. Kerman and Senol reported that the activity of

antioxidant enzymes is present in the hippocampal neural tissue. The results concluded that the reactive oxygen species have role in adverse events of EMR from radiation. On the other hand, melatonin has shown impact towards prevention of these effects [26].

DNA damage repair system

Genome integrity and maintenance during neural development is crucial. Therefore, strong mechanisms for DNA repair and preventing the regeneration are required [27]. It was believed that the adult human brain has low levels of DNA synthesis and repair; however, the knowledge about the brain DNA repair pathways increased in last two decades and unfolds the link between genomic DNA instability and neurodegenerative disorders. Most of the research revealed that the DNA damage is a direct mechanism of neurodegeneration and cause of neural death rather than degeneration [28,29]. Defect in the cellular pathways with defective DNA damage are common cause for the neural degeneration and hereditary human disorders. Defects in repair of single strand and double strand breaks are associated with many neurological onsets [30].

Table 1 shows some of these disorders and their definitive link with DNA repair system. Most of the neurodegenerative disorders are autosomal inheritance and categorized into three classes, namely, Nucleotide excision repair, Double Strand Break Repair (DBS) and Single strand Break Repair (SBS). As mentioned in the Table 1, Xeroderma pigmentosum, Cockayne's syndrome and Trichothiodystrophy are autosomal recessive disorders and happens due to the defect in Nucleotide excision repair. Ataxia telangiectasia, ataxia-telangiectasia-like disorder, Nijmegen breakage syndrome, Alzheimer's disease and Friedreich's ataxia occurred due to the defectiveness of double strand break repair. In these, Alzheimer's disease is an autosomal dominant and others are autosomal recessive. Spinocerebellar ataxias and Spinocerebellar ataxia with axonal neuropathy-1 are classified as single strand break repair, Spinocerebellar is an autosomal dominant disorder [29,31,32].

Table 1. *Neurodegenerative disorders and DNA repair defect (Table courtesy Rao et al. [29] and Rass et al. [31]).*

Disorder	DNA repair defect	Category of repair	Mode of inheritance
Xeroderma pigmentosum	NER (7 variants) pol n		
Nucleotide excision repair	Autosomal recessive		
Cockayne's syndrome	Defective NER and TCR	Nucleotide excision repair	Autosomal recessive
Trichothiodystrophy	ultraviolet-induced damage (ERCC2 and ERCC3 defects)	Nucleotide excision repair	Autosomal recessive
Ataxia and ataxia-telangiectasia-like disorder	Defective DNA damage response and DSB repair	Double strand break Repair	Autosomal recessive
Nijmegen breakage syndrome	Defective DNA damage response and DSB repair	Double strand break repair	Autosomal recessive
Alzheimer's disease	defective repair of oxidative damage and DSB repair	Double strand break repair	Autosomal dominant
Spinocerebellar ataxias	Expanded CAG repeats in various genes	Single strand break repair	Autosomal dominant
Friedreich's ataxia	GAA expanded repeats in *Frataxin* (*FXN*) gene	Double strand break repair	Autosomal recessive
Spinocerebellar ataxia with axonal neuropathy-1	Mutated DNA tyrosyl phosphodiesterase 1	Single strand break repair	Unknown

Table 2 showed a list of neurodegenerative disorders, respective genes that mutate and associated clinical features of the disorders. DNA Double Strand Break (DNA DSB) occurs by non-homologous end joining (proliferating and differentiated cells) or homologous recombination (proliferating cells) to maintain the integrity of DNA after DSB. The disorders caused due to the DNA DSB and the mutated genes are listed in Table 2. In DNA DSB, Microcephaly and immunodeficiency are the most common disorders. In Ataxia and Nijmegen breakage syndrome, cancer predisposition acts as a notable clinical feature [33]. DNA Single Strand Breaks (DNA SSBs) are most common features that occur due to the direct effect of Reactive Oxygen Species (ROS) and the repair action requires lesion-specific DNA glycosylase that could initiate the base excision [34]. In DNA SSB Spinocerebellar, ataxia with axonal neuropathy and Ataxia with oculomotor apraxia 1 are reported for neurodegenerative disorders, in which Cerebellar atrophy is a common clinical manifestation (Table 2). In addition to the DNA strand break repair, there is a DNA repair pathway which maintains the integrity of genomic DNA when damage occurs due to UV radiation. The Nucleotide Excision Repair (NER) pathway remains active in repairing the DNA damage at transcription level [35]. Xeroderma pigmentosum, Cockayne syndrome and Trichothyrodystrophy are the common disorders in NER, which are featured with UV-induced skin cancer,

peripheral neuropathy, progressive neurodegeneration and mental retardation, respectively (Table 2).

Table 2. Neurodegenerative disorders, mutated genes and clinical features. (Table courtesy: Madabhushi et al. [32] and McKinnon [33]).

Repair category	Disorder	Mutated gene	Clinical feature	Reference
DNA DSB deficiency	Ataxia-telangiectasia	*ATM*	Widespread cerebellar atrophy, immunodeficiency, cancer predisposition	[36]
	Ataxia-telangiectasia-like disorder	*MRE11*	Dysarthria, and occulomotor apraxia	[37]
	Nijmegen breakage syndrome	*NBS1*	Microcephaly, immunodeficiency and cancer predisposition	[38]
	ATR Seckel syndrome	*ATR*	Microcephaly, dwarfism	[39,40]
	LIG4 syndrome	*LIG4*	Microcephaly	[41,42]
	Human immunodeficiency with microcephaly	*XLF/Cernunos*	Microcephaly	[43]
	Fanconi anemia	*BRCA2*	Medulloblastoma	
DNA SSB deficiency	Spinocerebellar ataxia with axonal neuropathy	*TDP1*	Cerebellar atrophy	[44]
	Ataxia with oculomotor apraxia 1	*APTX*	Cerebellar atrophy, and cognitive impairments	[45]
NER deficiency	Xeroderma pigmentosum	*XP (A-G)*	Predisposed to UV-induced skin cancer, microcephaly, mental retardation, deafness, cerebellar ataxia, and peripheral neuropathy	[46-48]
	Cockayne syndrome	*XPB, XPD*	Developmental failure, premature aging, progressive neurodegeneration	[49,50]
	Trichothyrodystrophy	*XPD, XPB, TTD-A*	Brittle hair, Growth defects, photosensitivity, mental retardation	[51,52]

Conclusion

The overall picture suggests that oxidative stress is the major cause for the genomic instability in brain cells. However, there are still many questions remain since long. If oxidative stress is a predominant agent, then what is the role of antioxidants? Can they limit the oxidative stress? On the other hand, it is very clear that the DNA damage response is important during neural development. Therefore, determining specific factors and their contribution in DNA damage response in relation to neurodegenerative disorders is another major challenge. However, the role of mutations in DNA damage response is not a negligible factor which indirectly leads to the generation of reactive oxygen species. Over all, it is important to improve the understanding of DNA repair systems that are likely to provide new insights in development of therapeutic strategies and treatment methods to combat neurodegenerative disorders.

Over the years, advancements in biomedical research have been providing continuous breakthroughs in finding the role of oxidative stress related neurodegenerative clinical manifestations and aging disorders. As the exogenous and endogenous DNA damage factors increased, early diagnosis and treatment for neurological impairments became a grand challenge. Biomarkers for oxidative stress are continuously being tested to overcome this problem. However, model based effective programs are required to further improve our understanding in neurodegenerative disorders and design and develop the effective therapeutic approach.

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