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Neuroscience Reviews: DNA Double-Strand Breaks in the Human Brain

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Summary

DNA damage and mutations occur throughout the lifetime of neurons due to their high rates of oxygen metabolism, post-mitotic state and long life span. Exquisite molecular mechanisms have evolved to repair this damage. However, such repair is not always successful and the results can lead to neurodegenerative disorders.

Introduction

Despite the fact that nuclear DNA has evolved exquisite molecular mechanisms to repair and replicate itself, de novo point mutations often occur. In particular, the human brain carries considerable mutations that arise during fetal development and throughout the lifetime of each individual. Indeed, genome-wide scale studies indicate that neurons exhibit different rates of germline and somatic mutations within and between brain genomes. To compensate for the high rate and spectrum of mutations, several nuclear DNA repair mechanisms have also evolved in the mammalian nervous system to resolve specific DNA mutations or lesions. In this brief review, we discuss recent insights into the neurobiology of DNA double-strand breaks in the context of pathogenicity as well as with respect to molecular functionality.

What are DNA double-strand breaks?

DNA damage occurs throughout the entire lifetime of neurons due in part to their high rates of oxygen metabolism, post-mitotic state and relatively long life span (Brochier and Langley, 2013). At different stages of development, neurons are susceptible to DNA damaging factors that invariably impact broad scales of nucleotide sequences (Fig. 1). A fraction of these mutations are a source of selective (evolutionary) advantage, but in most cases, spontaneous occurring mutations can alter key cellular function contributing to major psychiatric and neurodegenerative disorders (see below). In this context, DNA double-strand breaks are a type of molecular lesion in which the double helix structure is physically broken at specific genomic loci (Price, 2013). This molecular breakage interrupts the

normal nucleotide sequence of exonic genes, thus limiting the availability of either DNA strand to fully participate in DNA replication (Schipler, 2013). It should be noted that DNA damage in the form of double-strand breaks arise spontaneously in the brain parenchyma as a result of ongoing neuronal activity (McKinnon, 2013; Torres et al., 2015). Thus, neurons undergo continuous remodeling cycles of DNA damage and DNA repair; distinct signaling pathways that are required for neural development.

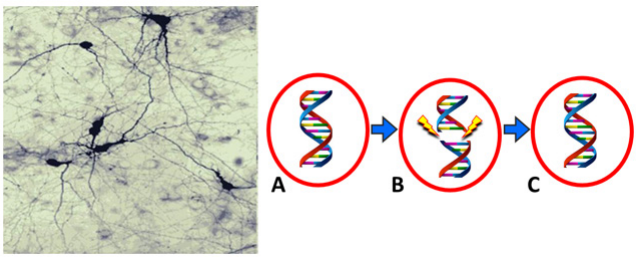

Fig. 1. Neurons contain an array of DNA repair pathways to ensure genome integrity (A). These repair pathways respond to specific types of lesions, such as DNA double-strand breaks (B). DNA lesions are then corrected by nucleotide excision repair pathways (C). However, if defects in DNA repair pathways occur during neural development, accumulation of DNA damage may directly lead to progressive disease pathology.

Why it matters?

While DNA double-strand breaks are widespread events in developing and mature nervous system landscapes (Torres et al., 2015), deficiencies in repair of nuclear and mitochondrial DNA damage have been linked to several neurodegenerative disorders. For example, Xeroderma Pigmentosum, Cockayne syndrome, Ataxia telangiectasia and Tricothiodystrophy are disease phenotypes that result from unavailable repair pathways that normally safeguard DNA integrity (Jeppesen et al., 2011; McKinnon, 2013; Madabhushi et al., 2014). Along the same lines, a lack of DNA double-strand break repair system has also been linked to Alzheimer's disease, Parkinson's disease and Amyotrophic lateral sclerosis (Madabhushi et al., 2014). Although these neuro-pathologies have different behavioral symptoms, their etiologies might share a conspicuous common feature, namely, neural genome instability.

What we know

Nuclear and mitochondrial DNA mutations are the sources of heritable diseases and evolutionary change. To minimize replicative and non-replicative DNA errors, genomes have evolved an array of DNA repair pathways in the nervous system. One of these pathways is the so-called non-homologous end-joint (NHEJ) pathway which repairs helix-distorting lesions such as those induced by ultraviolet radiation (McKinnon, 2013). If NHEJ is disrupted during neural development, defects might arise in the form of microcephaly and/or high-grade gliomas (Gilmore and Walsh, 2012). Another repairing pathway operating in the human nervous system is Ataxia telangiectasia, muted (ATM) which responds to DNA damage-responsive kinases. Of interest, disruption of ATM leads to progressive cerebellar ataxia and other neurodegenerative disorders characterized by widespread signaling dysfunction at the synapse (Suberbielle et al., 2013). The presence of these specific biochemical repair pathways highlights the importance of maintaining the DNA architecture, a prerequisite for molecular functionality and evolutionary fitness.

Next steps

DNA damage happens both during development and in the mature human brain (Fig. 2). DNA double-strand breaks also occur during the aging process, in particular, and may contribute to overall cognitive decline. Thus, understanding how DNA damage promotes pathology in the brain may allow for the development of rational, effective therapies for DNA repair-deficient syndromes.

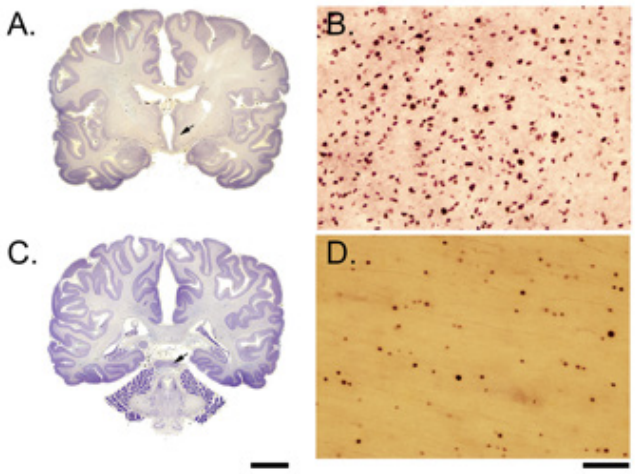

Fig. 2. Representative bright-field images of the human hypothalamus (B) and inferior colliculus (D) showing the distribution pattern of DNA double-strand breaks. The nuclear distribution of a DNA double-strand break marker (i.e., 53BP1) is widespread throughout the brain landscape. This suggests that DNA double-strand breaks are common, ongoing events spontaneously occurring in the normal brain. (A and C) illustrate the anatomical location of the photographed areas (arrows). Scale bars = 20 mm in (A) and (C); 100 μm in (B); 50 μm in (D). Adapted from Torres et al., 2015 (Neuroscience 290, 196-2013).

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Bibliographies

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Editor's Column

This 86th issue of the *Carrier* is another in our Neuroscience Reviews. Written by Mia P. Castiglione, Judith M. Horowitz, German Torres, it describes the phenomenon of DNA double strand breaks in human brain cells along with repair processes and possible consequences of non-repair of such breaks. It is both a timely and interesting article. We thank this group for again writing for this series.

I am writing this column just prior to the start of the presidential election primaries. In fact, the Iowa caucuses are just a few days away. What an amazing time we are living through. Obviously, the face of politics is changing, with both parties experiencing the outcomes of a failure to lead, to compromise and even to govern. Hopefully, the election outcomes and the outpouring of frustration and even anger by the electorate will give those on both sides of the isle pause to reconsider the rancor and partisanship that has marked the past several years in Washington.

In the latest issue of *Scientific American*[1] there was a very interesting article to which all of us should pay attention. Authored by Hathan Myhrvold who is founder and CEO of Intellectual Ventures, the article, titled "Even Genius Needs a Benefactor", makes the point strongly that without government funding, most basic research would come to an abrupt halt. Interestingly, he notes that many breakthrough inventions and discoveries made by now famous names in science and technology, such as Einstein and Edison, were not alone in their formulations and inventions. Rather, others were working along the same lines and hard on their heels. This phenomenon is known as parallel innovation is common in science and often drives us scientists to work hard to beat our "competition".

Unfortunately, he points out, many in seats of power take this as an argument for cutting or eliminating government support of basic research and letting the private sector fund such endeavors. After all, the private sector reaps the financial gains of putting the results of pure research into practical use.

However, Myhrvold points out that this is simply wrong. He and Bill Gates founded Microsoft Research, a very large industrial research laboratory with the clear understanding that basic research was not its mission. The research done there was to be focused on innovations that could be turned into revenue quickly. Most of us in our laboratories are focused on questions that have little practical or short-term utility, but gradually build on themselves to eventually paint a picture of a brain process, or an understanding of psychological function or how ant colonies function without a central planner. Without university, state and federal funding, this research would simply cease to exist.

Unfortunately, many emerging in politics now seem to look on basic research in this light, as an unnecessary expense that in light of seemingly more pressing spending needs should be reduced or even eliminated. We should all do what we can to counter this thinking. Support the NIH and NSF to your elected representatives at all levels. Should the "basic science not necessary" argument prevail in government, we all may see even bleaker days ahead.

On a personal note, we are back in Florida after a couple months at our second home in Dublin, Ohio and at our son's home in Michigan. We had a great holiday season and very good visits with our grandchildren (3 in Ohio and 2 in Michigan). Of course, this split between families there presents us with a real conundrum; whom do we root for in the big football rivalry, Ohio or Michigan.

If you want to pen an article for the Carrier, please contact me at the email below. There is an honorarium for each published article.

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