● PERSPECTIVE

DNA damage and neurodegeneration: the unusual suspect

Neurodegenerative diseases are caused by the loss of neuronal cells. As neurons deteriorate, a patient may experience relatively mild symptoms such as failing to name objects and people. However, with the progression of the disease, symptoms worsen resulting in loss of independence and a sense of "loss of oneself". Finally, the patient dies from a variety of complications.

For many years, researchers have been trying to find the causes and possible therapies for the diverse neurodegenerative pathologies. Yet, distinguishing between the causes and the consequences of neurodegeneration is difficult, as all the symptoms and markers get tangled in an array of phenotypes, such as changes in proteins, mRNAs or post translational modifications that behave differently in damaged brains. As of today, there is still no cure for neurodegeneration.

Alzheimer's disease (AD) is the most common among neurodegenerative diseases. When first discovered, AD patients' brains were found to have two main pathological marks: accumulation of amyloid β (Aβ), and neurofibrillary tangles formed by hyperphosphorylated tau protein. Later, a subset of familial AD was discovered in young patients (below 65-year-old), with mutations linking the familial AD to Aβ protein and its processing. Although familial AD patients – which represent less than 5% of all AD patients – are the only cases known to be Aβ-dependent, the hypothesis that Aβ has a crucial role in all AD patients has dominated the field for the last 30 years. Furthermore, there is no correlation between the severity of the disease and the presence and amount of Aβ plaques (Nelson et al., 2012). The second main mark of AD is hyperphosphorylated tau and the neurofibrillary tangles consequently formed. Tau has a key role in the stabilization of neuronal microtubules, yet its phosphorylated form was found to be cytotoxic. The affinity of tau to microtubules is altered by phosphorylation, hence affecting neuronal function. Additionally, phosphorylation stabilizes tau, which leads to the accumulation of cytotoxic protein aggregates in the cell (Ballatore et al., 2007). Moreover, a fragment of tau is nuclear and it seems to protect the DNA from genotoxic damage (Bukar Maina et al., 2016). Aside from AD, tau hyperphosphorylation is a common marker of other neurodegenerative diseases, among them frontotemporal dementia with Parkinsonism-17, Pick's disease and Huntington's disease.

Yet, although AD was first described more than a 100 years ago and it is being broadly investigated for more than 30 years, our understanding of AD causes and triggers, rather than its phenotypes, is still very poor. Research revealed, though, that the most important risk factor for AD and other neurodegenerative diseases is aging. The incidence of AD rises from about 3% in people younger than 70 years old to an estimate of 30–50% in people older than 85 years old.

Aging research has bloomed in the most recent years, with several molecular mechanisms affected. The most accepted theory of aging is that the accumulation of unrepaired DNA damage is the main cause: As we age, we accumulate DNA lesions. DNA damage occurs every day with an estimate of at least 10,000 insults per cell per day. It can be caused by endogenous processes such as metabolic byproducts, DNA replication and transcription, or by exogenous insults such as sun ultraviolet (UV) radiation, chemicals and pollution (Ciccia and Elledge, 2010). This raises the question: what is the fate of all of the non-repaired DNA as we age? Can it be the cause of an extensive list of age-related pathologies?

DNA carries all the information needed for an organism to exist. Therefore, keeping the DNA intact is one of the most important processes in a living cell. Many mechanisms evolved for safekeeping the DNA by repairing different types of damage, such as oxidation, deamination, single and double strand breaks and more (Ciccia and Elledge, 2010). Like any biological system, DNA repair is not perfect, and over the years the damage accumulates in the cells. When a cell crosses a damage threshold, it can lead to one of these pathways: (a) programmed cell death, in which an apoptotic response is activated; (b) senescence, in which the cell stops dividing, presents some morphological changes such as bigger size, and secretes pro-inflammatory cytokines; or (c) the cell keeps on dividing with damaged DNA as it fails to recognize unrepaired damage, increasing mutagenic rate and, in most cases, becoming cancerous.

Observations reveal that DNA damage accumulation is a widespread phenomenon in aged brains and it is even higher in pathological brains, such as in AD, Parkinson's disease and amyotrophic lateral sclerosis (ALS). The damage has been thought to be a consequence of the occurring pathological changes. Recent research in the field, however, reveals that it may be the other way around – DNA damage accumulation is the cause for neurodegeneration. This hypothesis is exemplified by the brain-specific deletion of SIRT6.

SIRT6, a chromatin-bound NAD^+-dependent histone deacetylase, is a transcription regulator that functions in many cellular processes such as stress responses, glucose and lipid metabolism, inflammation, tumor suppression and DNA damage repair (Kugel and Mostoslavsky, 2014). SIRT6 is involved in many DNA repair processes, in double-strand break repair – both homologous and non-homologous end joining pathways – but it is also potentially relevant in base-excision repair, mismatch repair and nucleotide excision repair (Kugel and Mostoslavsky, 2014; Chalkiadaki and Guarente, 2015).

SIRT6 deficiency in a mouse model resulted in progeria-like syndrome, and premature death by 3-4 weeks of age. Models with specific tissue deletion of SIRT6, showed its involvement as a tumor suppressor. Our recent study gives the first evidence for SIRT6 contribution as a neuroprotective protein, and the brain-specific SIRT6KO to be a good model for age-associated neurodegeneration (Kaluski et al., 2017). In this study, we demonstrate that brain-specific deletion of SIRT6 is a causative agent of a neurodegenerative phenotype as it provokes the accumulation of unrepaired DNA damage. Knocking out SIRT6 in mice brains resulted in a clear impaired learning phenotype similar to mouse models with

Tau-deficiency, cerebral irradiation, impaired learning and neurodegeneration (Lesné et al., 2006; Tanda et al., 2009; Graham and Sidhu, 2010; Roberson et al., 2011). At the cellular level, SIRT6-deficient brains presented increased signs of DNA damage, accompanied by increased apoptotic cell death.

One of the most intriguing results was the appearance of increased hyperphosphorylation and stability of tau in SIRT6 knock out (KO) brains. In addition, inducing DNA damage in wild type cells through irradiation led to similar phenotype as in SIRT6KO cells, indicating a relation between DNA damage accumulation and signaling to the development of stable and hyperphosphorylated tau. Interestingly, glycogen synthase kinase 3 (GSK3) – the known tau kinase – is activated in SIRT6KO brains and cells, and when DNA damage is induced by irradiation, it leads to tau stability and hyperphosphorylation. All these results are of particular relevance for AD, where SIRT6 protein is found in fairly low levels.

Moreover, other groups have shown that impairment of several other DNA damage repair enzymes causes a variety of neurodegenerative diseases. For example, the kinase ataxia telangiectasia mutated (ATM) is mutated in ataxia telangiectasia – a disease with a neurodegenerative phenotype. ATM is a critical DNA damage protein, phosphorylating hundreds of targets to activate the repair cascade of DNA double-strand breaks. Other examples include proteins Cockayne syndrome A (CSA) and Cockayne syndrome B (CSB), which are crucial for transcription-coupled nucleotide excision repair (TC-NER), and are mutated in Cockayne syndrome. Cockayne syndrome patients present premature aging and neurodegenerative symptoms (for a more comprehensive review see Madabhushi et al., 2014).

Overall, our and other studies imply that DNA damage is indeed the cause, rather than the effect, of neurodegeneration, and therefore efforts should be made to find molecules that can improve DNA repair enzymes activity. However, a careful balance needs to be achieved, since in some cases SIRT6 is protective, while in some types of cancer its overexpression is harmful (Chalkiadaki and Guarente, 2015).

To conclude, one of the most harmful types of stress that cells can probably undergo is DNA damage. While DNA damage was previously thought to be the result of different disorders and pathologies, it is now starting to be considered the driver for age-related diseases such as neurodegeneration.

As the human average life span has significantly risen in the last century and the trend continues, aging-associated pathologies are becoming more common. Therefore, increased effort should be made to better understand the proteins and pathways involved in DNA repair.

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