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Nucleotide excision repair in chronic neurodegenerative diseases

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ABSTRACT

Impaired DNA repair involving the nucleotide excision repair (NER)/transcription-coupled repair (TCR) pathway cause human pathologies associated with severe neurological symptoms. These clinical observations suggest that defective NER/TCR might also play a critical role in chronic neurodegenerative disorders (ND), such as Alzheimer's and Parkinson's disease. Involvement of NER/TCR in these disorders is also substantiated by the evidence that aging constitutes the principal risk factor for chronic ND and that this DNA repair mechanism is very relevant for the aging process itself. Our understanding of the exact role of NER/TCR in chronic ND, however, is extremely rudimentary; while there is no doubt that defective NER/TCR can lead to neuronal death, evidence for its participation in the etiopathogenesis of ND is inconclusive thus far. Here we summarize the experimental observations supporting a role for NER/TCR in chronic ND and suggest questions and lines of investigation that might help in addressing this important issue. We also present a preliminary yet unprecedented meta-analysis on human brain microarray data to understand the expression levels of the various NER factors in the anatomical areas relevant for chronic ND pathogenesis. In summary, this review intends to highlight elements supporting a role of NER/TCR in these devastating disorders and to propose potential strategies of investigation.

1. Introduction

Defects in genome maintenance, and in nucleotide excision repair (NER) pathway in particular, cause human pathologies associated either with high cancer predisposition and/or severe neurodevelopmental abnormalities. Rare inherited NER syndromes fall into two classes: xeroderma pigmentosum (XP) is dominated by a strong, sunlight-induced skin cancer predisposition and, in some patients, by accelerated neurodegeneration. Cockayne syndrome (CS), and related conditions such as trichothiodystrophy are characterized by severe neurodevelopmental abnormalities. Patients with the XP/CS complex have mixed symptoms and present with skin and eye disease of XP and the somatic and neurological abnormalities of CS [1]. These clinical observations lend support to the concept that defective NER might also play a critical role in chronic neurodegenerative disorders (ND), such as Alzheimer's and Parkinson's disease. This hypothesis is further substantiated by the evidence that aging is the principal risk factor for these diseases, and that NER is very relevant for the aging process itself [2]. A role of NER in the pathogenesis of AD and PD is also consistent with the notion that environmental factors are also critical in the onset of these neurodegenerative diseases, as NER deals with stochastic DNA damage, which is at least in part of environmental origin. In addition, because neurons are postmitotic cells and regeneration in the brain is very limited, it is perfectly conceivable that these cells require particular care for maintenance of genetic fidelity, and chronic defects in the machineries in charge might result in pathology.

Our understanding of the exact role of NER in chronic ND, however, is extremely rudimentary; while there is no doubt that defective NER can lead to neuronal death, evidence for its participation in the etiopathogenesis of ND is inconclusive thus far. Identification of pathogenic mechanisms and potential therapeutic targets is a topic of extreme relevance, especially in consideration of the anticipated social burden of ND in the fast-aging population of industrialized countries. Further focused investigations are therefore very pertinent and certainly required to unambiguously demonstrate a role of NER in these pathologies. In this review, we would like to summarize the experimental observations supporting a role for NER in chronic ND and to suggest questions and lines of investigation that might help in addressing this important issue.

2. Nucleotide excision repair

NER is divided into two pathways, GG-NER and TC-NER, which differ in the first step. The first branch is responsible for repair of

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the wide class of general helix-distorting lesions anywhere in the genome, while the second repairs lesions blocking the RNA polymerase activity and therefore elongation during transcription [3,4]. The spectrum of lesions eliminated by both systems is at least in part non-overlapping. TC-repair most likely involves additional and poorly characterized factors that might remove also transcription-blocking lesions caused by oxidation of the bases, which are not the substrate of GG-NER [5,6].

In GG-NER the protein XPC is believed to be the first main factor to bind damaged DNA [7]. XPC recognizes bulky distortions in the helix structure caused by the lesion and might act in concert with other accessory partners having diverse functions, which in some cases are still poorly understood. HR23, a homologue of Rad23 – which exists in two isoforms, HR23A and HR23B – is probably involved in XPC polyubiquitination, which might increase its affinity for DNA. CEN2 is an optional factor that may stabilize the complex [8,9]. The DDB complex, formed by XPE and DDB2, enhances DNA distortion to facilitate recognition by XPC [8]. Once the damage is recognized, XPC binds the repair/transcription factor TFIIH and facilitates its interaction with the lesioned DNA. The TFIIH factor consists of ten subunits, seven of which compose the core of the complex (XPD, XPB, p62, p52, p44, p34 and TTDA). Other three subunits (CDK7, MAT1, and Cyclin H) form the so-called *cyclin activating kinase-subcomplex*, which is connected to TFIIH core via interaction with XPD [10]. The TFIIH multimeric complex is stabilized by the XPG factor [11]. XPB and XPD are 5′-3′- and 3′-5′-DNA helicases respectively, which unwind the helix in proximity of the lesion [12]. This unwinding process separates the two DNA filaments and generates two short single strand stretches, which facilitate the recruitment of a further complex, composed by XPA, which has affinity for chemically altered DNA, and the ssDNA binding protein RPA1 which binds the non-damaged strand). The fundamental function of this pre-incision complex is to stabilize the open DNA structure [13,14].

The next step involves endonucleolytic cleavage and excision of the damaged and now uncoiled ssDNA. The process is performed by two endonucleases, the dimeric XPF-Ercc1 complex, which cuts at the 5′ end of the ssDNA, and the XPG factor, which cuts at the 3′ end [15]. This process results in a single stranded gap in the genome and a single stranded oligonucleotide fragment that is excised. The latter typically comprises 27–30 nucleotides.

The gap is filled by de novo synthesis of DNA by DNA-polymerase complexes that include polymerase δ, κ, and ε. These enzymes are recruited by the PCNA clamp in association with factors that are specific for the polymerase type. Polδ is recruited by RPA, the clamp loader RCF, and p66, while polε requires the CTF18-RCF clamp loader. Polκ is instead recruited by ubiquitinated PCNA and XRCC1 [16].

The final step is DNA ligation, which can be performed by two different enzymes. DNA ligase 1 operates exclusively during the S phase of the cell cycle, while DNA ligase IIIa-XRCC1 complex operates throughout the whole cell cycle [17].

TC-NER repairs lesions that block RNA polymerase II and therefore interfere with the vital process of transcription. TC-NER differs from GG-NER in the first step, recognition of the damage, which is carried out in TC-NER by the elongating RNA polymerase. Here, three proteins, CSB, CSA, and XAB2 are involved in poorly defined steps of making the lesion accessible to NER factors presumably by backtracking of the RNA polymerase and recruitment of XPG and TFIIH after which the remainder of the NER reaction may proceed as for GG-NER [18]. Indirect evidence supports the idea that transcription-blocking different than NER repaired ones are made accessible by CSB, CSA, XPG, and TFIIH to a different DNA repair process called base excision repair (BER). The latter deals with more subtle DNA damages that include many oxidative lesions. The total of TC-NER and presumed TC-BER is designated here as transcription-coupled repair (TCR).

Since GG-NER operates genome wide, defects in this subpathway result in broadly diffused accumulation of damage (except for the transcribed strand of active genes where TCR still takes care for lesion removal). As a consequence of global genome lesion accumulation, GG-NER defects lead to enhanced mutations and hence cancer; In fact, GG-NER defects are associated with the cancer syndrome XP. On the other hand, defects in TCR cause damage that interferes with transcription and favors cell death. Interestingly, impairment of TCR is strongly associated with the neurodevelopment abnormalities in CS, XP/CS and other CS-like syndromes and in the corresponding mouse models [19].

3. Neurodegeneration

Neurodegenerative diseases (ND) are characterized by a slow, chronic, and progressive neuronal loss. The latter, at least in initial stages of the pathogenesis, is confined to distinctive areas and affects only specific neurochemical types of neurons [20–23]. This regional specificity underlies the diverse symptomatology of the various ND, because different brain functional and anatomical domains command different abilities. These crucial features should not be neglected in investigations aimed to identify novel pathogenic mechanisms because neuronal death is an endpoint that might be caused by multiple and converging detrimental cascades. Not every deleterious mechanism belongs to the etiopathogenesis of ND and, while derangement in certain processes (e.g. NER/TCR) might lead to neuronal loss, this does not necessarily imply that the process itself is intrinsic to the ND pathobiology. Involvement in ND pathogenic cascades should be therefore inferred upon unambiguous evidence that perturbation of the considered mechanism reproduces pathological hallmarks of chronic ND and leads to physiological alterations recapitulating human diseases. Assays to address mechanisms' participation in pathogenesis should be performed in reference to a panel of appropriate and reliable indicators that confirm affinities with human ND. The choice of such markers, however, has been a source of contention for long time. An intrinsic problem is that, despite sharp differences in clinical manifestations, different ND also share several functional defects. Mitochondrial dysfunction, altered protein homeostasis, redox imbalance, and calcium dysregulation are only some examples of anomalies observed in all major chronic ND [24–26]. These processes, however, are rather vulnerable per se; accordingly, their alteration is observed in many conditions that have little, or nothing to do with chronic ND [27,28] and thus they rather reflect a general state of ongoing pathology. Accordingly, they are also associated with broader signs of distress, which interest neuronal and non-neuronal cells and include dystrophic neurites and activation of astrocytes and microglia [29]. This concept obviously applies to NER as well and, while defective DNA repair might certainly elicit neurological alterations, the question whether this is enough to state unambiguously that it is relevant for chronic ND remains open.

In this respect, assessing regional specificity of cellular dysfunctions might unambiguously point out the relevance of a mechanism for ND pathogenesis. In fact, at least in initial stages, cell death is confined to distinctive areas and interests only specific neurochemical types of neurons. For instance, in Parkinson's disease, only neurons using dopamine degenerate, and only in the *substantia nigra pars compacta*. This feature underlies the diverse symptomatology of the different neurodegenerative diseases, because brain anatomical domains govern different functions. It is important to highlight that neuropathology and its anatomical pattern are highly dynamic and evolves and spreads in the course of the diseases