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Clinical implications of the basic defects in Cockayne Syndrome and xeroderma pigmentosum and the DNA lesions responsible for cancer, neurodegeneration and aging

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Abstract

Cancer, aging, and neurodegeneration are all associated with DNA damage and repair in complex fashions. Aging appears to be a cell and tissue-wide process linked to the insulin-dependent pathway in several DNA repair deficient disorders, especially in mice. Cancer and neurodegeneration appear to have complementary relationships to DNA damage and repair. Cancer arises from surviving cells, or even stem cells, that have down-regulated many pathways, including apoptosis, that regulate genomic stability in a multi-step process. Neurodegeneration however occurs in nondividing neurones in which the persistence of apoptosis in response to reactive oxygen species is, itself, pathological. Questions that remain open concern: sources and chemical nature of naturally occurring DNA damaging agents, especially whether mitochondria are the true source; the target tissues for DNA damage and repair; do the human DNA repair deficient diseases delineate specific pathways of DNA damage relevant to clinical outcomes; if naturally occurring reactive oxygen species are pathological in human repair deficient disease, would anti-oxidants or anti-apoptotic agents be feasible therapeutic agent?

Introduction

DNA repair deficiencies have been linked to three major clinical outcomes: cancer, neurodegeneration and aging. Each outcome is associated with different combinations of pathways of DNA damage and repair, and with a corresponding different set of human hereditary diseases. The human repair deficient diseases xeroderma pigmentosum (XP) and Cockayne syndrome (CS) have specific phenotypes of cancer and neurodegeneration, but their relationship to premature aging is not clear, although their fibroblasts do not senesce prematurely in vitro (Cleaver, 1984). XP patients have not been followed in sufficient numbers to know whether they age prematurely, apart from their cancer burden. CS patients show a neurological and developmental degeneration that differs from normal aging, but is described as a segmental progeroid (Nance and Berry, 1992). Cancer, neurodegeneration and aging are therefore different pathological outcomes of repair deficiencies that will require different therapeutic approaches.

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Most DNA repair deficiencies result in some form of cancer, if not in human then in the corresponding mouse mutants, as was evident from the earliest association of nucleotide excision repair (NER) with skin cancer in XP (Cleaver, 1968; Cleaver, 1969; Friedberg et al., 1998). Human diseases that link DNA repair to cancer include: mismatch repair (MMR) associated with colon cancer; human patients with mutations in *MUTYH* and mice that have both *Mutyh* and *Ogg1* deleted are predisposed to colorectal cancer (David et al., 2007); DNA double strand break (DSB) repair with lymphomas in ataxia telangiectasia (AT) and related disorders (Barzilai et al., 2002); NER with skin cancer in XP (Cleaver and Mitchell, 2005); homologous recombination with breast cancer through the familial breast cancer genes *BRCA1* and Fanconi anemia (*FANCD1/BRCA2*) genes (McKinnon and Caldecott, 2007); crosslink repair with leukemia in Fanconi anemia (FANC) genes (McKinnon and Caldecott, 2007).

What are the sources and chemical nature of naturally occurring DNA damaging agents?

The default explanation for DNA damage from endogenous sources is that reactive oxygen species (ROS) from mitochondrial leakage is the major culprit (Wallace, 2005). A direct test of a mitochondrial source for nuclear damage, however, failed to support the idea (Hoffmann et al., 2004). The question remains whether mitochondrial ROS themselves, or longer-lived products such as oxidized proteins, lipids, sugars and nitroso compounds migrate sufficiently to reach the nuclear DNA. ROS include an exceedingly complex spectrum of products, many at low concentrations in many different classes of macromolecules (Barzilai et al., 2002). ROS generate many singly modified bases such as 7,8-dihydro-8-oxoguanine (8-oxo-G) that are substrates for base excision repair (BER) (David et al., 2007), and oxidized purine products (5′,8-purine cyclodeoxynucleosides) that require NER for their repair and block transcription (Brooks et al., 2000; Kuraoka et al., 2001). Lipid oxidation products produce malondialdehyde-deoxyguanosine (M-1-dG) adducts in DNA that block transcription (Cline et al., 2004). Analysis in a cell-free system showed that although UV-induced pyrimidine dimers and single strand breaks (SSBs) were effective blocks to transcription, base damage of the kind subject to BER were not (Kathe et al., 2004).

ROS plays important signaling functions in inflammation and neural signaling. Cellular responses to ROS may therefore represent a delicate balance between the production of necessary ROS for tissue growth and differentiation, the suppression of excess ROS by antioxidants such as glutathione and catalase, and repair of ROS-induced DNA damage. In *S cerevisiae*, for example, different oxidizing agents require different, almost non-overlapping, sets of genes for resistance, few of which represent DNA repair genes (Birrell et al., 2001; Game et al., 2003; Thorpe et al., 2004). Due to the complexity of cellular sources of ROS, and their potential involvement in normal cell signaling processes, the relative sensitivity of various genetic disorders to a range of oxidizing agents is still unclear.

Variations in the severity of CS symptoms between patients have not yet been related to the sites of mutation, and complete loss of CSB results in a milder phenotype than many point mutations (Horibata et al., 2004). The presence of mutant misfolded CSA or B proteins might therefore be as important in CS as protein aggregates are in other neurological diseases (Ciechanover and Brundin, 2003). Variations could also occur in cellular antioxidants or ROS production by different mitochondrial haplotypes (Wallace, 2005). CSB protein functions in chromatin remodeling (Newman et al., 2006); CSA & B are required for ubiquitylation of RNA pol II (Lee et al., 2002); CSA is a cofactor for E3 ubiquitylation ligase that may target many proteins (Groisman et al., 2003). These many additional functions could also contribute to the range of clinical symptoms.

DNA damage and repair in aging?

Aging has been variously associated with many parameters, but there may be subtle differences between life-span, that is genetically determined and is species specific, and aging that is associated with functional decline in various tissues often associated with pathologies such as cancer. The insulin-dependent growth factor pathway (IGF-1/GH) plays an important role in energy metabolism and life-span in many species (Hansen et al., 2005). Although the basal metabolic rate would consequently be expected to cause variations in ROS, no influence on spontaneous mutagenesis could be detected (Lanfear et al., 2007). An RNAi screen in *C elegans* for genes that regulate life-span generated many genes in endocrine and metabolic pathways but few DNA repair genes (Hansen et al., 2005). Even so, DNA repair does seem to be rate limiting for stem cell renewal in the hematopoeitic system, due to accumulation of unrepaired damage while in the quiescent state (Rossi et al., 2007a; Rossi et al., 2007b).

Several repair deficient diseases show deficiencies in the IGF-1/GH axis: the Xp-d mouse with the human trichothiodystrophy (TTD) mutation (de Boer et al., 2002), knockouts in the 5′ NER nuclease Xpf and Ercc1 (Niedernhofer et al., 2006), and Csb (van der Pluijm et al., 2006). This may represent unrepaired damage to specific tissues such as liver and pancreas. The first DNA repair knockout was in *Ercc1* in which the liver showed evidence of DNA damage and elevated p53 levels (McWhir et al., 1993). A critical decline in the p53 response to DNA damage with age has recently been shown (Feng et al., 2007), but here as in so many examples the question remains which is the cause and which is the consequence of the aging process.

DNA damage and repair in neurodegeneration

Three groups of repair deficient disease have distinctive neurodegenerative phenotypes: the NER diseases of XP and CS, the cerebellar ataxias associated with SSB repair, and diseases associated with DSB repair and damage-dependent signaling (Table 1) (McKinnon and Caldecott, 2007). These all appear to be recessive conditions that show wide ranges of clinical severity even within a single disease. Parents have few reported symptoms, implying that the relevant repair systems in normal individuals have excess capacity for dealing with endogenous levels of damage. Premature aging is featured in individual diseases among all of these classes, showing no consistent mechanism relating DNA damage to aging. These classes all appear to share common elements of degeneration of the central nervous system especially the cerebellum and Purkinje cells (Kohji et al., 1998;Hayashi, 1999;Hayashi et al., 2001;Cleaver, 2005;Hayashi et al., 2005;Laposa et al., 2007a;McKinnon and Caldecott, 2007) that show high sensitivity to oxidative damage (Leech et al., 1985;Otsuka and Robbins, 1985;Barlow et al., 1999;Hayashi et al., 2001;Sun et al., 2001;Reichenbach et al., 2002;Chen et al., 2003;de Waard et al., 2003;Goldbaum and Richter-Landsberg, 2004;Liu et al., 2006).

Recent studies have shown that differentiation of neurons is associated with up-regulation of ROS and down-regulation of antioxidants (Tsatmali et al., 2005). This would put a heavier demand on cells' capacity to repair ROS damage during differentiation, just when a reduction of overall NER appears also to occur (Nouspikel and Hanawalt, 2000). There is some evidence that premature entry of neuronal cells into the cell cycle can trigger cell death (Herrup et al., 2004; Kruman, 2004) by a mechanism involving recruitment of Pol beta instead of replicative polymerases (Copani et al., 2007), which would be exacerbated by unrepaired neuronal damage (Nouspikel and Hanawalt, 2003). No evidence for premature DNA replication was found in a mouse model of Cs-b with severe neurodegeneration (Laposa et al., 2007a). There remains, however, limited knowledge of repair systems in specific areas of the brain, in contrast to other models of differentiation (Nouspikel and Hanawalt, 2000; Nouspikel and Hanawalt, 2006).

Do the human DNA repair deficient diseases delineate specific subsets of DNA damage relevant to clinical outcomes?

A self-evident observation is that cancer arises in tissues with proliferative potential, whereas neurodegeneration occurs in post-mitotic brain tissue. Therefore a unifying principle for damage-dependent neurodegeneration would be the prediction that deficits in TCR and SSB repair should lead to increased apoptosis of post-mitotic neurons, especially since single strand breaks are also transcription blocking lesions (Kathe et al., 2004). Neurodegeneration might be ascribed to the greater relative importance of a TCR-like repair in differentiated brain cells such that a failure of TCR triggers an apoptotic response (Ljungman and Zhang, 1996; Proietti De Santis et al., 2002; D'Errico et al., 2003). Increased apoptosis has been demonstrated for TCR deficits (Ljungman and Zhang, 1996). Since apoptosis would remove damaged cells from the skin in CS patients this phenotype would, conversely, prevent UV carcinogenesis (D'Errico et al., 2005).

Neurodegeneration appears to be mainly associated with TCR deficits and GGR deficits more extensively with cancer (Cleaver, 2005). A recent suggestion that RNA pol II is a universal sensor of DNA damage (Lindsey-Boltz and Sancar, 2007) blurs the distinction between TCR and global repair. The neurological symptoms of CS patients have been ascribed to defective repair in the brain of endogenous oxidative damage that blocks transcription (Kuraoka et al., 2000; Osterod et al., 2002; de Waard et al., 2003; Kyng et al., 2003; Tuo et al., 2003; Cline et al., 2004), but the more common oxidative base damages (8-oxo-G, 5-hydroxycytosine, thymine glycols) do not block transcription and are therefore not the culprits in neurodegeneration (Kathe et al., 2004). CSA and CSB cells are however different in their responses to oxidative damage, despite overlap in clinical symptoms (de Waard et al., 2004; D'Errico et al., 2007). The oxidative lesion 8-oxo-G does not appear to accumulate in CS autopsy material (Hayashi et al., 2005) despite the higher amounts of protein oxidation and lipid oxidation in the brains of CS patients (Hayashi et al., 2001) and crossing Cs-b mice with Ogg1 deficient mice did not enhance the neurological symptoms (Laposa et al., 2007b). Surprising is the absence of reported neurological or aging phenotypes among mouse strains lacking glycosylases which are the recognition and excision enzymes for BER that would be expected to show increased sensitivity to ROS (Friedberg et al., 1998), although many oxidative base damages are not transcription blocking lesions (Kathe et al., 2004). Perhaps these strains should be screened more carefully, or combined strains made lacking several glycosylases to increase the chances of detecting such a phenotype.

Most XP-E, XP-C or XP-V patients do not have clinically reported neurodegeneration, and evidence for life-shortening is difficult to obtain due to the profound influence of wide variations in solar exposure and clinical care. There is one report of an XP-C patient with autism (Khan et al., 1998) and one of an XP-V patient with neurological symptoms (Hessel et al., 1992), but neurological symptoms in these groups are rare. XPE and XPC are mainly involved in damage recognition in nontranscribing DNA and XPV/Pol eta in replicating damaged DNA. Therefore loss of these functions should have little impact on differentiated brain tissue that is predominantly nondividing and heavily dependent on TCR. Crossing Cs-b mice with Xp-c mice, however, strongly enhanced the neurological symptoms showing that XPC is not without some relevance to neurological maintenance (Laposa et al., 2007b). Some evidence suggests that XPC is required for repair of oxidative damage that might be necessary in the brain (Kassam and Rainbow, 2007). The WRN protein, a helicase defective in the specific aging disorder Werners syndrome facilitates replicative bypass by Pol eta (Kamath-Loeb et al., 2007), so some association of the XP-V and Werners phenotypes could be expected to impact lifespan.

These considerations suggest that the presently unidentified causative DNA lesions for neurodegeneration should be strong transcription blocks, but poorer substrates for NER, BER or blocks to the replicative polymerases (Cleaver, 2005).

What constitutes feasible therapeutic targets?

The critical question is whether, now that we have extensive knowledge of the molecular biology and genetics of the repair deficient diseases, does this help the patients? One simple approach that did not need extensive basic research is for XP patients to reduce their skin cancer risks by avoiding sun exposure, although even here there is still uncertainty as to how rigorous this needs to be and the relative roles of UVA and UVB and the contribution of competing reactions such as production of vitamin D (Garland et al., 1990; Weinstock et al., 1992) that is reported to increase NER efficiency (Gupta et al., 2007). A recent example of the role of protection is seen in a Guatemalan population with a founder XPC mutation in which limited sun protection and clinical care results in death around the age of 10, whereas similar XPC mutations have much less influence on lifespan in the US (Cleaver et al., 2007).

Neurodegeneration is a more difficult matter. Consideration of the large number of potential protein targets of the ATM, ATR and CHK2 kinases, the possibility of identifying clinically relevant targets is daunting (Smolka et al., 2007). Several potential points of attack are conceivable: premature entry into the cell cycle, the proteasomal pathway, apoptosis and ROS. Each of these has been investigated in model systems with various degrees of success, but few have yet emerged from clinical trials as strong candidates. The strongest evidence for a biological role for ROS comes from treatment of mice with antioxidants that have achieved life extension as well as reduced neurodegeneration (Heidrick et al., 1984; Holloszy, 1998; Meydani et al., 1998). Treatment of Atm mice with antioxidants has shown promising success in reducing Purkinje cell damage and improving behavioral endpoints (Chen et al., 2003; Gueven et al., 2006). Another option would be the use of anti-apoptotic or cell-cycle arresting agents, although the persistence of cells with oxidative damage might lead to a different form of pathology.

The neurodegenerative symptoms in mice are generally milder than in human and the cancer burden higher, especially for Cs (van der Horst et al., 1997; van der Horst et al., 2002; Laposa et al., 2007b) and Xpa (Berg et al., 1997; De Vries, 1997; Tanaka et al., 2001). Variations due to strain backgrounds are also factors, especially regarding life-shortening versus cancer risk (Li et al., 2007; Partridge and Gems, 2007). The Cs-b strain that has been most extensively used (van der Horst et al., 1997; Laposa et al., 2007b) contains a truncation mutation that may resemble the mild human UV-sensitive disorder associated with an early truncation in CSB that lacks neurodegeneration (Horibata et al., 2004), unlike most CSB patients with amino acid changes and termination mutations scattered throughout the gene. There is consequently a need for further mouse models especially those that recapitulate the mutations causing severe CS clinical disorders.

There is a major regulatory hurdle that needs to be faced regarding clinical trials in human repair deficient patients. There are so few patients that trials are almost impossible to design to satisfy safety and effectiveness criteria. The difficulties experienced with development of a DNA repair cream for skin cancer in XP patients (Yarosh et al., 2001) exemplifies the difficulties facing treatment of complex disorders of neurodegeneration in rare patients. One possibility would be to test drugs and antioxidants that have already been approved by FDA for use in Alzheimers, Parkinson's and other more common neurological disorders. Developing therapeutic approaches is most challenging when translating bench knowledge to patients' benefit.

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Table 1

Major diseases of DNA repair, the repair pathways and pathology

DNA repair pathways[1]	Syndrome and common abbreviation[2]	Gene name[3]	Phenotype
GGR/NER	Xeroderma pigmentosum (XP)	*XPE* *XPC*	-Photosensitivity -Skin cancer
NER common pathway	Xeroderma pigmentosum (XP)	*XPA* *XPB* *XPD* *XPF* *XPG*	-Cerebellar degeneration -Photosensitivity -Skin cancer
NER common pathway	Trichothiodystrophy (TTD)	*XPB* *XPD* *TFB5*	-Photosensitivity -Hair and immune deficiency -Life-shortening (mouse)
Bypass polymerase	Xeroderma pigmentosum variant (XPV)	Pol eta	-Photosensitivity -Skin cancer
TCR	Cockayne syndrome (CS)	*CSA* *CSB*	-Retinal, cerebellar (purkinje), ganglial calcifications, -Aging
TCR	UV sensitive syndrome (UV^S)	*CSB*	-Mild photosensitivity
TCR	Cerebro-oculo-facio-skeletal syndrome (COFS)	*ERCC1* *CSB*	-Severe neonatal lethal developmental disorder
BER	Ataxia-oculomotor apraxia syndrome (AOA)	*APTX*	-Cerebellar ataxia -Oculomotor apraxia
Topoisomerase-1 induced breaks (TCR)	Spinocerebellar ataxia with axonal neuropathy (SCAN1)	*TDP1*	-Postmitotic neurons (cerebellar ataxia and axonal neuropathy)
NHEJ and V(D)J recombination	Severe combined immunodeficiency with sensitivity to ionizing radiation (RS-SCID)	*DCLRE1C*	-Immunodeficiency -Photosensitivity
NHEJ	LIG4 syndrome (LIG4)	*LIG4*	-Microcephaly -Lymphoreticular disease -Immunodeficiency
NHEJ	Severe combined immunodeficiency with microcephaly (SCID)	*NHEJ1*	-Microcephaly -Immunodeficiency -Growth retardation
BER	Werner syndrome (WRN)	*WRN*	-Photosensitivity -Premature aging -Premature arteriosclerosis -Diabetes mellitus -Scleroderma-like skin changes
DSB repair and signal transduction	Ataxia telangiectasia (AT)	*ATM*	-Cerebellar ataxia -Oculomotor apraxia -lymphocytic leukemia
DSB repair and signal transduction	Ataxia-telangiectasia-like disorder (ATLD)	*MRE11*	-Cerebellar ataxia -Oculomotor apraxia
DSB repair and signal transduction	Nijmegen breakage syndrome (NBS)	*NBS1*	-Microcephaly,

DNA repair pathways[1]	Syndrome and common abbreviation[2]	Gene name[3]	Phenotype
			-Growth retardation -Immunodeficiency -Cancer predisposition
ATR signaling pathway	Seckel syndrome 1 (SCKL1)	*ATR* *SCKL2* *SCKL3*	-Microcephaly -Growth retardation -Mental retardation
ATR signaling pathway	Microcephaly primary autosomal recessive 1 (MCPH1)	*MCPH1* *MCPH2* *MCPH4*	-Microcephaly
NHEJ and V(D)J recombination	Inactivation of Ku70 or Ku80 in mouse models	*Ku70* *Ku80*	-Premature aging -Cancer predisposition -Lymphomas

[1] Abbreviations not already defined in the text include: ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia mutated and Rad3-related; NHEJ, nonhomologous end joining; V(D)J, regions of the immunoglobulin locus involved in rearrangements.

[2] Abbreviations shown in parenthesis represent the common abbreviations for each disease. Ku70, Ku80 are two end binding proteins associated with DSB repair.

[3] The initials represent the common designations for each gene(s) involved in the corresponding disease.