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Relationship Between DNA Damage and Energy Metabolism: Evidence from DNA Repair Deficiency Syndromes

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1. Introduction

It is estimated that the human genome incurs on the order of $1,000$-1,000,000 DNA lesions/cell/day (Lodish 2000). A majority of these are thought to be due to endogenous sources, including reactive oxygen and nitrogen species (ROS, RNS) that can oxidize cellular macromolecules including lipid, protein and nucleic acid. These free radicals can be generated for specific purposes by cellular enzymes; for example, nitric oxide synthases generate NO in endothelial cells for signaling purposes, while NADPH oxidase and myeloperoxidase generate ROS in granulocytes to kill invading pathogens. However, ROS can also occur as a byproduct of cellular energy metabolism (Beckman and Ames 1998). Most cells use mitochondrial respiration as a means of energy production. The process of moving electrons across the mitochondrial membrane can at some frequency result in their transfer to molecular oxygen and the generation of superoxide and hydrogen peroxide, which together can generate the highly reactive hydroxyl radical and damage nearby molecules, including DNA.

The frequency of superoxide formation is influenced by many factors, including the rate of electron transport and the capacity of the mitochondria to couple the proton gradient created across the inner membrane to ATP production, or to dissipate it in the form of heat through the use of uncoupling proteins. High rates of electron transport and efficient ATP production or uncoupling are consistent with reduced ROS generation, while low rates of transport or inefficient ATP production (for example when ATP/ADP ratios are already high) are consistent with increased ROS generation. Different substrates may also influence mitochondrial ROS production. Oxidation of ketone bodies, for example, may generate more ROS than oxidation of acetyl CoA from glucose (Tieu et al. 2003). Substrate utilization further depends on cell type and nutritional status. For example, neurons prefer to oxidize glucose, but can also use ketone bodies derived from fat oxidation in the liver. Skeletal muscle can use either fat or glucose, depending on availability, but tends to use one at the exclusion of the other (Randle et al. 1963). In cooperation with mitochondria, peroxisomes also play a major role in energy metabolism by oxidizing long-chain fatty acids. Peroxisomes can further participate in ketogenesis, amino acid oxidation and the oxidative phase of the pentose phosphate pathway depending on substrate availability. Like mitochondria, they are a major

source of ROS and RNS generating enzymes, and thus a potential source of oxidative macromolecular damage by leakage of ROS/RNS across the organelle membrane. Mitochondria and peroxisomes also produce abundant amounts of antioxidants enzymes such as superoxide dismutase and catalase to neutralize ROS. Thus, mitochondria and peroxisomes can both contribute to ROS as well as play a role in ROS detoxification.

In order to generate energy efficiently, cells oxidize carbon units derived from glucose, amino acids or fatty acids in mitochondria. The use of these substrates is governed by nutritional status and is further subject to hormonal control. Insulin and glucagon are major regulators of organismal substrate utilization. In the fed state, elevated blood glucose promotes insulin secretion by the pancreas and transport of glucose into insulin-responsive tissues including liver, muscle and fat. In the liver, glucose is stored as glycogen or used as a substrate for *de novo* lipogenesis. Insulin signaling also inhibits release of free fatty acids from white adipose tissue and promotes *de novo* lipogenesis and dietary lipid repackaging in the liver for storage in white adipose tissue. After a meal, glucose levels fall and counter-regulatory hormones such as glucagon reverse the actions of insulin and glucose by promoting hepatic glycogenolysis and gluconeogenesis for glucose-dependent tissues such as red blood cells and neurons, and release of fatty acids from the white adipose tissue for oxidation in other organs. Defects in insulin signaling caused by overeating are associated with a spectrum of pathologies including diabetes, obesity and atherosclerosis collectively known as the metabolic syndrome. Although the underlying mechanisms are not entirely clear, it is associated with chronic inflammation and oxidative stress (Hotamisligil 2006). In stark contrast to metabolic syndrome is the spectrum of phenotypes associated with dietary restriction (DR, also known as calorie restriction), defined as reduced food intake without malnutrition. Originally described in rodents to reduce the incidence of cancer and extend lifespan (McCay, Crowel, and Maynard 1935), DR has proven efficacy at increasing lifespan, stress resistance and metabolic fitness in a wide range of experimental organisms. In mammals, the DR state is characterized by reduced serum glucose, reduced growth factors and growth factor signaling, improved insulin sensitivity, increased resistance to oxidative stress and reduced adiposity (Fontana and Klein 2007). While the molecular mechanisms underlying the benefits of DR remain unclear, reduced steady state levels of macromolecular oxidative damage suggest reduced ROS production and/or increased antioxidant defenses play a role.

When DNA damage occurs, there are a number of overlapping repair pathways that recognize and remove the damage, as well as a battery of signaling pathways that influence immediate decisions on cell fate and longer-term adaptations to stress. DNA damage repair pathways are distinguished in large part by the lesions that they recognize. Oxidative base lesions are typically recognized by the base excision repair (BER) pathway, while bulky helix distorting lesions are typically removed by the nucleotide excision repair (NER) pathway. Although the latter is chiefly responsible for removal of UV lesions from sunlight, endogenous oxidative lesions are also partially dependent on NER pathways (Brooks et al. 2000). Oxidative stress can also cause breaks in the sugar-phosphate backbone, resulting in single strand breaks that can interrupt transcription or replication. When the density of such breaks is high, they can occur nearby on opposite strands and result in double strand breaks. Such lesions can be repaired by homologous recombination in the presence of a sister chromatid (for example during S phase of the cell cycle) or by non-homologous recombination during other phases of the cell cycle when the sister chromatid is not readily available to serve as a template for repair. The so-called DNA damage response (DDR) is

not a single response but a network of signaling and repair pathways activated by genotoxic stress. Upon DNA damage such as a double strand break or a collapsed replication fork, the serine/threonine kinases ATM or ATR, respectively, initiate a cascade of cellular responses resulting in cell cycle arrest and recruitment of repair factors. One of the targets of ATM and ATR is the tumor suppressor p53, which is stabilized by phosphorylation and activates transcription of genes involved in cell fate, including apoptosis or senescence. Other proteins such as poly ADP ribose polymerase (PARP) are activated by DNA damage and can have indirect effects on cell fate decisions by depleting ATP and NAD+.

Given the connection between production of ROS by cellular metabolism and DNA damage, one might predict coordinate regulation of the cellular response to DNA damage and growth and metabolism on the cellular and organismal levels. In this chapter, we will discuss existing evidence of such a connection. First, we will consider metabolic changes associated with defects in NER disorders and their resemblance to the adaptive response to DR, particularly in mouse models of these diseases. Next, we will consider metabolic changes in a variety of other DNA damage repair and signaling disorders, ranging from DR-like phenotypes to metabolic disorder. We will conclude by reviewing the evidence linking DNA damage repair and signaling pathways directly and indirectly to changes in cellular growth and energy metabolism.

2. Metabolic defects in nucleotide excision repair deficiency syndromes

Although the mutations causing the segmental progerias Cockayne syndrome (CS) and trichothiodystrophy (TTD) are known, how alterations in the associated nucleotide excision DNA repair proteins cause pleiotrophic disease symptoms including dwarfism and cachexia are not yet clear. In mouse models of these disorders, unrepaired endogenous DNA damage is linked to perturbations in energy metabolism and alterations in insulin/insulin-like growth factor-1 (IGF-1) signaling. Paradoxically, these changes resemble beneficial adaptive responses to DR associated with improved metabolic fitness and extended longevity. In this section, we will discuss perturbations in growth and energy metabolism associated with defects in NER proteins in human disease and mouse models, and the potential role of DNA damage in eliciting these changes.

2.1 Cockayne syndrome and trichothiodystrophy

NER is an evolutionarily conserved pathway required for the removal of UV-induced DNA damage. It is divided into two branches based on how the lesion is initially recognized. Global genome (GG)-NER can occur anywhere in the genome upon recognition of DNA helical distortions by the XPC/HR23B/CEN2 complex. Transcription-coupled (TC)-NER occurs only on the transcribed DNA strand and is initiated by the stalling of an elongating RNA polymerase, for example by steric hindrance at the site of a bulky adduct. TC-NER specific proteins CSA and CSB participate in the upstream events surrounding the stalling of an RNA polymerase at the site of DNA damage. Although both CSA and CSB are involved in ubiquitination and protein turnover – CSA is a component of a ubiquitin ligase complex (Groisman et al. 2003), and CSB contains a ubiquitin-binding domain required for UV damage repair (Anindya et al. 2010) - their exact roles in TC-NER remain unclear. Once the TC-NER or GG-NER machinery recognizes the lesion, the helicases XPB and XPD unwind the damaged DNA, allowing validation of the lesion by XPA, endonuclealytic cleavage of

the phosphodiester backbone by XPG and XPF-ERCC1 and removal of the damaged oligonucleotide in preparation for repair DNA synthesis.

Mutations in CSA, CSB, XPG, XPD and XPB are associated with CS, a rare progressive disease characterized by photosensitivity, dwarfism, loss of subcutaneous fat and neurodegeneration. CS was first described by Edward Cockayne in 1936 (Cockayne 1936). To date, approximately 200 cases have been reported in the literature (Nance and Berry 1992; Ozdirim et al. 1996; Pasquier et al. 2006; Rapin et al. 2006). Despite UV sensitivity, CS is not associated with an elevated risk of skin cancer as observed in the related NER deficiency syndrome xeroderma pigmentosum (XP). Although there is a range in the onset and severity of CS, typical presentation involves normal in utero growth and birth weight followed by a profound postnatal growth failure within the first two years. This growth failure is also observed in the postnatal brain, resulting in developmental microcephaly and cognitive impairment. Neuropathological defects include demyelination and atrophy of white matter, calcification of the basal ganglia, cerebellar atrophy, demyelination of peripheral nerves, retinopathy, and neuronal loss in the inner ear (Weidenheim, Dickson, and Rapin 2009). Based on the involvement of white matter, CS is considered a form of leukodystrophy. Interestingly, such white matter diseases can be caused by various genetic defects in lysosome or peroxisome metabolism and typically present postnatally after normal birth and early development (Kohlschutter et al. 2010). Diabetes mellitus, early hypertension and atherosclerosis are also prevalent in CS (Rapin et al. 2006). Besides the nervous system and adipose tissue, other organ systems appear proportionately smaller in size yet unimpaired (Weidenheim, Dickson, and Rapin 2009). Death occurs around 12 years of age often from cachexia or an intercurrent illness such as respiratory infection.

The fact that weight is more affected than height in CS led to the use of the term cachexia, or wasting, in association with this disease (Nance and Berry 1992). Although it is not clear that lean mass is preferentially affected as is typical with cachexia, adipose tissue is clearly affected. CS is classified as a lipodystrophy, indicating the abnormal redistribution of fat. Subcutaneous fat loss leads to sunken eyes and a wizened appearance that are further defining characteristics of the disease. Adipocytes are a major site of energy storage in the form of triglycerides, as well as a source of lipokines involved in a variety of processes including appetite control, immune function and temperature regulation. CS patients presumably still have functioning adipocytes that can produce adipokines but do not store triglycerides for reasons that remain unclear. This is distinct from generalized lipoatrophy, in which adipocytes and associated adiopkines are lost, resulting in hyperlipidemia and insulin resistance despite the paucity of fat. Interestingly, lipids are also a major component of myelin sheaths that are lost in CS, although no connection between altered lipid metabolism and demyelination has been reported.

The cause of dwarfism in CS is not known; however there are no consistent data to suggest alteration of endocrine function (Rapin et al. 2006; Nance and Berry 1992). For example, growth hormone (GH) levels are normal to elevated. Whether or not transient perturbation of GH/IGF-1 signaling, which has been reported in mouse models (see below), is relevant in the human disease remains unknown.

Mutations in XPD and XPB, as well as another TFIIH component, p8, can cause another photosensitivity disorder with characteristic growth failure and neurological involvement known as TTD (Morice-Picard et al. 2009). Unlike CS, TTD patients present with characteristic brittle hair and nails caused by a transcriptional defect in terminally differentiating keratinocytes. Despite this difference, there are many similarities between

the diseases as would be expected if they share a common basis in defective transcription-coupled DNA repair. As with CS, TTD shows no increase skin cancer risk despite photosensitivity. TTD patients also demonstrate dysmyelination and lipodystrophy. Despite the hypothesis that CS and TTD share a common basis in defect transcription-coupled DNA repair (Andressoo, Hoeijmakers, and Mitchell 2006), this is by no means the only hypothesis regarding the etiology of these diseases. For example, the requirement for the CAK complex of TFIIH in the phosphorylation and regulation of nuclear hormone receptors, which play a major role in cellular and organismal metabolism, has led to the competing hypothesis that disease symptoms are caused by defects in gene expression regulated by these transcriptional activators (Compe et al. 2007; Keriel et al. 2002; Brooks, Cheng, and Cooper 2008).

2.2 Mouse models of NER progeria

Mouse models of CS engineered by disabling the CSA or CSB genes share some characteristics of human CS but in a milder form. Knockout mice are born normally, but are photosensitive and display an age-dependent loss of photoreceptor cells (van der Horst et al. 2002; van der Horst et al. 1997). Although they develop normally, CSB mice remain lean in adulthood and have normal lifespans (Dolle et al. 2006). Interestingly, CSA and CSB mice are resistant to renal ischemia reperfusion injury, a form of acute oxidative and inflammatory stress, and display improved glucose tolerance and insulin sensitivity (Susa et al. 2009). Both of these phenotypes are typical of DR mice (Mitchell et al. 2009). TTD mice created by mutating residue 722 from an R to a W in the XPD C terminus faithfully recapitulate the brittle hair phenotype of the human TTD, but like the CS mice have an overall milder phenotype than the corresponding human disease (de Boer et al. 1998). TTD mice display end of life pathologies consistent with both accelerated aging (osteoporosis, aortic sarcopenia, lymphoid depletion) as well as DR (reduced inflammatory dermatitis, reduced pituitary adenoma, reduced subcutaneous fat) (Wijnhoven et al. 2005). Duodenal epithelial hyperplasia has been proposed to play a role in reduced food absorbance leading to the overall DR-like phenotype (Wijnhoven et al. 2005). XP-CS mice, engineered with a different point mutation in the XPD gene (G602D) associated in patients with the symptoms of both CS and XP also recapitulate the mild features of mouse CS as well as the severe skin cancer susceptibility of XP (Andressoo et al. 2006).

Another group of mouse models of NER deficiency share a more severe core phenotype of dwarfism, ataxia, failure to thrive and death before weaning at 3-4 weeks of age. This so-called "NER progeria" was first described in mice lacking the endonuclease Ercc1 (Melton et al. 1998; Weeda et al. 1997) and subsequently in a number of genetic models of NER deficiency, including CSB/XPA (Murai et al. 2001), XPA/TTD (de Boer et al. 1998), XPA/XPCS (Andressoo et al. 2006), CSB/XPC (Laposa, Huang, and Cleaver 2007) double homozygous mutants as well as XPG (Sun et al. 2003) and XPF (Tian et al. 2004) single homozygous mutants.

Common metabolic features of NER progeria in mice include reduced blood glucose and reduced insulin, disproportionate reduction of white adipose tissue weight, and accumulation of triglycerides in the liver (van de Ven et al. 2007). Although the cause of death is not clear, animals may inevitably succumb to hypoglycemia. Reduced food intake does not seem to be the cause of metabolic perturbations. Liver transcriptome analysis of *Ercc1-/-* and CSB/XPA mice revealed altered expression of genes involved in carbohydrate and oxidative metabolism and peroxisome biogenesis suggestive of increased glycogen

synthesis, decreased glycolysis, and decreased oxidative metabolism (Niedernhofer et al. 2006). Global metabolic profiling by NMR revealed that *Ercc1-/-* mice have altered lipid and energy metabolism and a shift toward ketosis when compared to age-matched controls (Nevedomskaya et al. 2010). *Ercc1-/-* mice show several metabolic adaptations that resemble those seen in DR, including decreased LDL and VLDL, increased HDL, and decreased serum glucose (Nevedomskaya et al. 2010).

Another common feature of NER progeria that may underlie the growth retardation is reduced mRNA and serum protein expression of IGF-1 (Niedernhofer et al. 2006; van der Pluijm et al. 2007; van de Ven et al. 2006). Unlike long-lived endocrine deficient dwarfs (Ames, Snell) with reduced GH secretion due to defective anterior pituitary development (Bartke and Brown-Borg 2004), NER-deficient mice have an intact pituitary and normal to elevated GH levels, consistent with normal hypothalamic and pituitary function. Instead, GH receptor mRNA levels are reduced in multiple tissues, resulting in reduced GH-dependent IGF-1 production. Liver transcriptome analysis confirmed a general downregulation of multiple components of the postnatal GH/IGF-1 axis. Nonetheless, in select mouse models of severe NER progeria, effects on serum IGF-1 and glycemic index can be transient, occurring prior to weaning but normalizing in animals that survive this apparent developmental bottleneck (van de Ven et al. 2006).

Global profiling of gene expression in liver confirmed a significant overlap between NER progeria and long-lived dwarfism (Schumacher et al. 2008) consistent with the physiologic data. Paradoxically, the core feature of IGF-1 signaling attenuation increases lifespan in several species (Rincon et al. 2004; Longo and Finch 2003) but is associated with decreased longevity in NER progeria. Altered growth and energy metabolism has thus been interpreted as an adaptive response to endogenous genotoxic stress. Whether or not this response is maladaptive in this model is not known, but does appear to be so in mouse models of models of Hutchinson-Gilford progeria syndrome (HGPS) (Marino et al. 2010) as discussed below.

2.3 Evidence for a role of DNA repair in CD and TTD phenotypes

What is the evidence that defects in DNA repair, and in particular TC-NER, are causative of the pleiotropic disease symptoms including disturbances in growth and energy metabolism? Most NER proteins associated with disorders in man and mouse are multifunctional with distinct roles in several different cellular processes. For example, CSB was originally cloned as a TC-NER factor, but can also function in chromatin remodeling, transcriptional initiation (Le May, Mota-Fernandes et al. 2010), transcriptional elongation (Le May, Egly, and Coin 2010), BER via interactions with the BER glycosylase Ogg1 and stimulation of APE1 incision (Wong et al. 2007) and rRNA synthesis (Bradsher et al. 2002). Similarly, the TFIIH complex containing the XPB and XPD helicases plays a role in transcriptional initiation and activated transcription by a subset of nuclear hormone receptors (Keriel et al. 2002; Compe et al. 2007). Roles for many of these functions have been proposed to be causative of one or more symptoms of CS, TTD or XP. However, due in large part to the high degree of overlap between symptoms in multiple different mouse models, where the effects of homozygous mutations can be interrogated against a standardized genetic and environmental background, it has been hypothesized that these conditions have a common underlying cause (Andressoo, Hoeijmakers, and Mitchell 2006; van de Ven et al. 2007). Currently, the only known common function of each of the proteins, including CSA, CSB, XPD, XPB and XPG, is the transcription-coupled arm of NER. Based on current data, this makes a defect in

TC-NER a plausible cause of overlapping disease symptoms, but does not rule out common pathways that are currently unknown or untested for all relevant disease loci.

If indeed defects in the TC-NER pathway are causative of disease symptoms, what are the relevant endogenous DNA lesions? Most of what is known about the function of TC-NER proteins is derived from cell-based experiments with UV as the source of DNA damage. UV irradiation produces two types of bulky lesions which are substrates for NER; cyclobutane pyrimidine dimers, mainly removed by TC-NER and pyrimidine 6-4 pyrimidone photoproducts, typically processed by GG-NER. Indeed, cells deficient in CSB fail to repair cyclobutane dimers but repair 6-4 photoproducts efficiently (Barrett et al. 1991). UV light may possibly damage keratinocytes of CS patients, but has little capacity to induce lesions in other relevant tissues. Most bulky lesions are induced by exogenous sources, but some bulky lesions are created by endogenous sources (De Bont and van Larebeke 2004).

8,5'-cyclopurine-2'-deoxynucleaosides (cyPudNs) are endogenous lesions formed in DNA by the hydroxyl radical (Jaruga, Theruvathu, et al. 2004; Dizdaroglu et al. 1987). cyPudNs are chemically stable lesions which are expected to accumulate slowly and are candidates for lesions which could cause neurodegeneration (Kuraoka et al. 2000; Brooks 2008). cyPudNs block transcription and, unlike most oxidative DNA lesions, cyPudNs are repaired by NER rather than BER (Brooks et al. 2000; Kuraoka et al. 2000). *In vitro* assays using CHO and NER-deficient CHO cells show that ERCC1 and XPG are required for excision of the 8,5'-(*S*)-cyclo-2'deoxyadenosine (cyclo-dA) lesion, while BER glycosylases are not active on the cyclo-dA lesion (Brooks et al. 2000). Using a host cell reactivation assay, Brooks et. al. found that cyclo-dA is a substrate for NER *in vivo* (Brooks et al. 2000). Oxidative lesions are elevated in and may contribute to neurodegeneration (Kruman 2004). TC-NER may protect neurons from oxidative lesions, the accumulation of which may lead to the neuronal death observed in CS. Nonetheless, it remains controversial whether or not cells from CS patients or mice are hypersensitive to oxidative stress (van de Ven et al. 2006). Thus despite the growing literature on molecular functions of CSA, CSB and other TC-NER proteins, proof that unrepaired endogenous oxidative lesions cause CS and/or TTD is lacking. Identification of such a lesion and its target tissue awaits.

3. Metabolic defects in other DNA repair and maintenance disorders

A number of human syndromes and mouse models with defects in DNA damage repair and signaling also display perturbations in growth and energy metabolism. Some of these show characteristics of adaptive changes reminiscent of DR as described above in TC-NER syndromes, while others display insulin resistance and atherosclerosis resembling metabolic syndrome on the opposite end of the energy spectrum. In this section, we will describe a number of syndromes and/or mouse models with known defects in DNA repair, genome maintenance or DNA damage-related signal transduction with an emphasis on changes in growth, energy metabolism, adiposity and glucose homeostasis.

3.1 Hutchinson-Gilford Progeria Syndrome

Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare autosomal dominant progeria characterized by failure to thrive, growth retardation unrelated to GH deficiency, baldness and decreased body fat without insulin resistance (Merideth et al. 2008). Atherosclerosis is thought to result from the general accelerated aging observed in all tissues and organs rather than from elevated serum lipoproteins (Al-Shali and Hegele 2004). Vascular disease

and stroke are the main causes of death in HGPS, with a life expectancy of about 13 years of age (Merideth et al. 2008). HGPS is caused by a mutation in Lamin A, a component of the nuclear envelope, which leads to a truncated protein missing the Zpmste24 cleavage site (Merideth et al. 2008).

Mouse models deficient in Zmpste24 exhibit nuclear architecture abnormalities, severe growth retardation, loss of subcutaneous adipose tissue, accumulation of lipid in ectopic sites such as liver, and premature death (Pendas et al. 2002; Varela et al. 2005). Aberrations in cardiac muscle of Zmpste24 mice include thinning of the ventricular wall, muscle degeneration, increased inflammation and interstitial fibrosis, suggesting that cardiomyopathy and heart failure contribute to death in this model (Pendas et al. 2002). Zmpste24 mice exhibit increased autophagy in skeletal muscle, possibly due to decreased circulating glucose and insulin and increased adiponectin, resulting in AMPK activation and suppression of the mTOR pathway (Marino et al. 2008). Gene expression data of livers of Zmpste24 mice indicate a shift from glucose to lipid metabolism, a response also seen in starvation (Marino et al. 2008). Zmpste24 mice show decreased IGF-1 and GHR expression in the liver, along with suppressed levels of IGF-1 and increased levels of GH in the serum (Marino et al. 2010). Treatment of Zmpste24 mice with recombinant IGF-1 using a subcutaneous minipump rescues some of the progeroid phenotypes, resulting in improved body weight, increased subcutaneous fat, reduced kyphosis and reduced alopecia (Marino et al. 2010). Serum GH levels were restored (reduced to normal) and lifespan of Zmpste24 mice was expended by 18% by IGF-1 treatment (Marino et al. 2010). Thus, chronic perturbation of the somatotroph axis in response to defects in nuclear architecture has been interpreted as a maladaptive response that actually accelerates disease symptoms.

Does nuclear architecture have any impact on DNA damage repair or signaling? Evidence for a connection between nuclear architecture and DNA damage comes from cells of Zmpste24 deficient mice. These cells display increased chromosomal abnormalities and γ-H2AX phosphorylation indicative of greater DNA damage and reduced genomic stability (Liu et al. 2005). Fibroblasts from HGPS patients senesce prematurely, indicating a cell-autonomous alteration in proliferative capacity (Bridger and Kill 2004; Allsopp et al. 1992). Thus, alterations in nuclear architecture leading to chromosome instability can indirectly activate the DNA damage response (Liu et al. 2005; Verstraeten et al. 2007).

3.2 Werner syndrome

Werner syndrome is a segmental progeria characterized by short stature, early graying and loss of hair. There is no evidence for endocrine deficiency as an explanation for growth deficiency (Monnat 2010). Type 2 diabetes mellitus and dyslipidemia leading to atherosclerosis are also common features of Werner syndrome. Patients with Werner syndrome typically live into their mid-50s and die from premature cardiovascular disease or cancer (Huang et al. 2006; Martin 1985). Werner syndrome patients show accelerated brain accumulation of amyloid β peptide and hyperphosphorylated tau, both common in age-associated disorders (Leverenz, Yu, and Schellenberg 1998). Werner syndrome is also associated with loss of myelin fibers in both the central and peripheral nervous system (Umehara et al. 1993) although without the significant delays in neuronal development observed in CS. Werner syndrome is caused by a defect in Werner (WRN), a Rec-Q helicase which hydrolyzes ATP to separate double-stranded DNA for replication, recombination, transcription and repair (Monnat 2010). The WRN protein is also essential for maintaining chromosomal integrity through intact recombination or DNA replication (Monnat 2010).

Many features of Werner syndrome are faithfully recapitulated in a mouse model in which the WRN gene is lacking the helicase domain (WRN$^{\Delta hel/\Delta hel}$) (Huang et al. 2006; Lachapelle, Oesterreich, and Lebel 2011). WRN$^{\Delta hel/\Delta hel}$ mice have elevated levels of ROS and oxidative DNA damage in liver and heart, and elevated serum triglycerides, glucose and insulin; all of which return to wildtype level upon long-term vitamin C treatment (Lebel et al. 2010). WRN appears to play a role in protecting cells from oxidative damage, and the loss of WRN leads to changes resembling the metabolic syndrome.

3.3 Ataxia Telangiectasia
Deficiency in the DNA damage sensor ATM (Ataxia Telangiectasia Mutated) leads to ataxia telangiectasia (A-T). A-T is a rare autosomal disorder characterized by cerebellar ataxia, elevated cancer incidence, immune dysfunction and elevated sensitivity to ionizing radiation (Shackelford 2005). The life expectancy for patients with A-T is roughly 20 years (Chun and Gatti 2004). A-T patients display signs of premature aging as well as insulin resistance and lowered insulin receptor affinity (Lavin 2000). Mouse models of ATM deficiency show an age-dependent increase in blood glucose and decrease in insulin sensitivity, consistent with a conserved role of this protein in metabolic function (Miles et al. 2007). In an *ApoE$^{-/-}$* mouse model, haploinsufficiency of ATM leads to accelerated atherosclerosis and multiple features of metabolic syndrome relative to the *ApoE$^{-/-}$* mouse (Mercer et al. 2010).

3.4 Seckel syndrome
Stalled replication forks activate A-T and Rad-related protein (ATR), which leads to cell cycle checkpoint activation. Defective ATR signaling in humans causes Seckel syndrome, characterized by growth retardation and severe microcephaly (O'Driscoll and Jeggo 2008). While growth hormone secretion is normal, Seckel syndrome features high circulating IGF-1 levels and slightly decreased binding affinity for the IGF-1 receptor (Ducos et al. 2001; Schmidt et al. 2002). Whether this represents a constitutive defect in IGF-1 signalling or an adaptive response to a defective DNA damage response remains unknown.

3.5 TP53
Activation of the tumor suppressor p53 by genotoxic or other forms of stress can trigger various outcomes that reduce the chance of a damaged cell progressing into a tumor, ranging from cellular senescence to apoptosis. Besides its role in the response to genotoxic stress, p53 plays a central role in cellular energy metabolism through regulation of oxidative phosphorylation, glucose transporter expression and fatty acid synthase (Zhang, Qin, and Wang 2010). Mice engineered with defects in p53 are highly cancer prone, but also display a number of metabolic phenotypes. For example, phosphorylation of p53 at Ser18 by ATM is an important regulator of glucose homeostasis, as a S18A mutation renders mice insulin resistant (Armata et al. 2010). p53 is activated in adipose tissue upon high fat diet-induced obesity and insulin resistance in mice; inhibition of p53 in adipose tissue rescues senescence and insulin resistance in diabetic mice (Minamino et al. 2009). Taken together, these data suggest that p53 activation, for example by oxidative stress derived from over-nutrition and potentially by isolated DNA damage, can promote the onset of metabolic syndrome.

3.6 DNA-PK, KU

DNA-PK, Ku70 and Ku80 form a complex at double strand breaks to facilitate non-homologous end joining (NHEJ). Mice deficient in the catalytic subunit of DNA-PK (DNA-PKcs) exhibit accelerated aging, growth defects and decreased lifespan (Espejel et al. 2004). Mice deficient in Ku80 display premature aging symptoms including osteopenia, atrophic skin, hepatocellular degeneration and age-specific mortality; *Ku70-/-* mice display growth retardation (Gu et al. 1997; Vogel et al. 1999). Increased lymphoma and defects in B and T cells of DNA-PK, Ku70 and Ku80 mice are attributed to their lack of NHEJ resulting in deficient V(D)J recombination required for adaptive immunity; however, premature aging phenotypes are not seen in Rag-1 (V(D)J deficient) mice and thus not related to the lack of adaptive immunity and associated inflammation (Holcomb, Vogel, and Hasty 2007). Reduced size in Ku80 mice is not due to reduced IGF-1, but may instead be related to defects in cell-autonomous proliferation (van de Ven et al. 2006).

3.7 NEIL1 DNA glycosylase deficiency

NEIL1 glycoslyase is the homologue of the bacterial formamidopyrimidine DNA glycolyslase and initiates repair of oxidative lesions in BER, acting specifically on 2,6-diamino-4-hydroxy-5-formamidopyrimidine and 4,6-diamino-5-formamidopyrimidine lesions (Jaruga, Birincioglu, et al. 2004). A mouse model deficient in NEIL-1 glycosylase develops severe obesity, dyslipidemia, fatty liver disease and hyperinsulinemia in the absence of exogenous oxidative stress (Vartanian et al. 2006). The development of metabolic syndrome in *NEIL1-/-* mice is accelerated on a high-fat diet, indicating NEIL1 absence renders mice more susceptible to oxidative stress-induced metabolic syndrome (Sampath et al. 2011). Although no human diseases are associated with deficiency of NEIL1, several polymorphisms of NEIL1 with different activities on oxidized bases are found in humans (Roy et al. 2007). Whether or not these polymorphisms may lead to susceptibility to metabolic disease is not understood.

3.8 SIRT6

SIRT6 is the mammalian homologue of yeast Sir2 and is an NAD-dependent histone deacetylase. SIRT6 was originally described as a component of the BER system, as SIRT6 deficient MEFs are hypersensitive to BER-lesion inducting agents such as methyl methanesulfonate and hydrogen peroxide; sensitivity was restored to that of wildtype by introducing the dRP lyase domain of Polβ (Mostoslavsky et al. 2006). Although no direct interaction between SIRT6 and BER factors has been reported to date, SIRT6 appears to impact DNA repair by stabilizing chromatin and facilitating DNA-PK dependent damage signaling (Lombard 2009; McCord et al. 2009). SIRT6 also influences metabolism both by deacetylating histone H3 lysine 9 and by repressing HIF1α to control the expression of glycolytic genes, which explains the glucose imbalance seen in SIRT6 knockout mice (Zhong et al. 2010). The SIRT6 phenotype is predominantly a metabolic one, with mice developing normally, although smaller than wildtypes, until 2 weeks of age, when they suffer from a degenerative wasting and severe hypoglycemia resulting in death (Mostoslavsky et al. 2006). Like NER progeria, SIRT6 knockout mice also have reduced serum IGF-1, likely contributing to their small size. Neural-specific deletion of SIRT6 does not rescue the postnatal growth failure, but does rescue the severe hypoglycemia that leads to death in full-body knockouts of SIRT 6 (Schwer et al. 2010; Mostoslavsky et al. 2006). Neural-specific

SIRT6 mice survive much longer than the whole-body knockouts, and by one year of age become obese (Schwer et al. 2010).

Syndrome	Affected gene	Metabolic feature
Cockayne Syndrome	CSA/CSB	Loss of subcutaneous fat
Trichothiodystrophy	XPB/XPD/TTDA	Loss of subcutaneous fat
Hutchinson-Gilford Progeria Syndrome	Lamin A	Loss of subcutaneous fat, atheroslcerosis
Werner Syndrome	WRN	Lipid accumulation in blood, insulin resistance
Ataxia telangiectasia	ATM	Insulin resistance
Seckel syndrome	ATR	Increased IGF-1

Table 1. Human DNA repair diseases resulting in aberrant metabolism.

4. Cell culture models

In cultured cells, a number of recent studies on gene expression, signal transduction and protein interaction networks upon genotoxic stress point to both direct and indirect links between various forms of DNA damage and pathways regulating growth and energy metabolism.

In mammals, organismal growth and metabolism are controlled by availability of nutrients and energy, which in turn influence secretion of circulating regulatory hormones including insulin from the pancreas, growth hormone from the pituitary, and growth-hormone dependent IGF-1 from the liver. Cellular responses to nutrients, energy and growth factor availability are controlled at the cell surface by receptor tyrosine kinases including the insulin receptor (IR) and IGF-1 receptor (IGF-1R). Binding of peptide hormones to their cognate receptors activates a signal transduction cascade resulting in the phosphorylation and activation of downstream kinases including AKT and mTOR. AKT exerts control over energy metabolism by phosphorylating and inactivating FOXO transcription factors as well as TSC1, a major negative regulator of mTOR. mTOR activation, which requires growth factors as well as nutrients (amino acids) and energy, results in phosphorylation and activation of ribosomal protein S6 kinase, promoting protein translation and increased cell size and growth. mTOR also phosphorylates and inactivates the translational repressor eIF-4E-binding protein 1 (4EBP1), further promoting protein synthesis.

The role of protein kinases in DNA repair and the DDR is firmly established. In response to ionizing radiation, DNA damage response proteins ATM and ATR phosphorylate checkpoint kinases Chk1 and Chk2, as well as p53 to block cell cycle progression (Stokes et al. 2007). The kinase DNA-PK, a PI3-type protein kinase in the same family as ATM and ATR, is directly involved in the repair of DNA double strand breaks through the process of NHEJ. However, each of these kinases can target additional substrates involved in growth and energy metabolism outside of canonical DNA repair and damage signaling pathways in response to growth factor stimulation. For example, DNA-PK is recruited by the upstream-stimulatory factor to the promoter of fatty acid synthase (FAS), the master regulator of fatty acid synthesis, upon insulin stimulation (Wong et al. 2009). DNA-PK is required for transient DNA breaks at the FAS promoter and transcription of FAS (Wong et al. 2009). ATM is required for phosphorylation of 4EBP1 on Ser 111 to promote protein anabolism

upon insulin stimulation (Yang and Kastan 2000). This may be due indirectly to phosphorylation and inactivation of the mTOR repressor TSC2 by ATM (Alexander et al. 2010; Yang and Kastan 2000). ATM is also required for IGF-1 stimulated phosphorylation (activation) of AMPK, a cellular sensor of energy activated by low ATP/AMP ratios, to suppress energy-demanding processes such as cell growth in PANC and HeLa cells (Suzuki et al. 2004). ATM is also capable of inhibiting the stress signaling kinase JNK, whose activity is linked to several features of the metabolic syndrome (Schneider et al. 2006). Recently, ATM has been shown to be involved in the activation of autophagy through inhibition of mTOR (Alexander et al. 2010). DNA damage response proteins thus appear to be important regulators of cell growth and energy metabolism in response to environmental cues such as nutrient availability.

Importantly, there is mounting evidence that DDR proteins can also control these same metabolic pathways in response to DNA damage. One of the first clues was that ATM regulates expression of the IGF-1R in response to ionizing radiation (Peretz et al. 2001). Subsequent analysis of the ATM and ATR substrate pathway following ionizing radiation revealed several connections to the insulin-IGF-1-AKT pathway, including previously unidentified substrates insulin receptor substrate 2 (IRS2), AKT3 and its regulators HSP90 (heat shock protein 90) and PP2A (protein phosphatase 2A) (Matsuoka et al. 2007). Downstream targets of AKT including the transcription factor FOXO1, TSC1, S6K and 4E-BP1 were also identified as ATM and/or ATR substrates (Matsuoka et al. 2007). Cells lacking ATM demonstrate elevated mTOR and glycerophospholipid pathways when exposed to ionizing radiation (Varghese et al. 2010). Upon UV irradiation, DNA-PK is also required for translational reprogramming by directly or indirectly targeting the amino acid deprivation sensor GCN2 (Powley et al. 2009). The net outcome of this signal transduction cascade is to reduce general translation while at the same time to increase translation of proteins involved in adaptation to DNA damage, including NER proteins.

In addition to direct effects on cellular metabolism, activation of the DDR can trigger senescence-associated inflammatory cytokine secretion including IL-6 that can have an indirect effect on metabolism (Rodier et al. 2009). In 3T3-L1 adipocytes, for example, IL-6 inhibits phosphoenolpyruvate carboxykinase, which is required for triglyceride biosynthesis, thus increasing fatty acid mobilization (Feingold et al. 2011).

Another target of DNA damage-induced signal transduction is the tumor suppressor p53. p53 is normally a short-lived protein, but stabilization by phosphorylation promotes its activity as a transcriptional activator of cell-cycle inhibitors such as p21. p53 is stabilized as a result of multiple forms of stress, including genotoxic stress from ionizing radiation, ultraviolet radiation and ROS. In addition to cell cycle targets, p53 targets include genes involved directly in glycolysis (repression of phosphoglycerate mutase, (Kondoh et al. 2007)), and indirectly in respiration (activation of synthesis of cytochrome oxidase 2, a factor involved in COX assembly (Matoba et al. 2006)). In both cases, loss of p53 results in an increased glycolytic rate and decreased oxidative metabolism as is typically seen in cancer cells. TIGAR, another p53 target, is activated by low levels of stress and functions to repress glycolysis and to increase flux through the pentose phosphate pathway, resulting in increased generation of reduced glutathione, reduced ROS levels and protection from apoptosis (Bensaad et al. 2006). In some cells, glucose utilization by glycolysis competes with the pentose phosphate pathway responsible for generating NADPH reducing equivalents. Because NADPH is required for production of one of the major cellular antioxidants, reduced glutathione, increased glycolysis can come at the expense of

increased, rather than decreased, ROS. However, it is worth pointing out that this may be cell-type specific, as in other cells reduced glycolysis results in increased apoptosis.

ATR may be the kinase responsible for phosphorylating and stabilizing p53 in response to genotoxic stress (Colman, Afshari, and Barrett 2000). ATR is recruited to stalled replication forks by the single strand DNA binding protein RPA and the ATR-interacting protein ATRIP. Single-stranded DNA regions serve as a platform for RPA-ATRIP-ATR recruitment in the context of stalled elongating replication machinery (Ljungman 2007). p53 can be also be stabilized even in the absence of DNA damage by inhibiting transcriptional elongation by RNA PolII (Bode and Dong 2004; Ljungman 2007). Thus, lesions that block an elongating RNA PolII and activate TC-NER can also signal through p53. Interestingly, the production of UV-induced DNA damage foci in quiescent fibroblasts requires ATR and is defective in primary cells from patients with Seckel syndrome (O'Driscoll et al. 2003).

In cells deficient in TC-NER, unrepaired UV-induced lesions cause downregulation of both the GHR and IGF-1R (Garinis et al. 2009). This is consistent with the finding in NER progeroid mice of reduced insulin/IGF-1 signaling (Niedernhofer et al. 2006; van der Pluijm et al. 2007; van de Ven et al. 2006), and suggests that this effect can be cell autonomous *in vivo* rather than driven primarily by neuronal or neuroendocrine control. Interestingly, downregulation of growth receptors upon UV treatment was not inhibited *in vitro* by inhibitors of AKT, MAPK or JAK, but whether it requires DDR signaling through ATM, ATR or DNA-PK is not reported (Garinis et al. 2009). The identity of the signaling pathway from the lesion to receptor downregulation is currently not known.

In addition to impacting cellular metabolism by activating signal transduction pathways, DNA damage repair pathways can also directly affect cellular energy status. PARP is activated upon oxidative base damage and consumes both ATP and NAD+ in the polyadenylation of various local substrates (Gagne et al. 2006), thus reducing available cellular energy currencies. Depending on the amount of damage and level of PARP activation, cellular energy stores can be depleted to pathological levels resulting in cell death. In the absence of exogenous DNA damage, PARP ablation results in increased NAD+ levels and increased activation of the NAD+-dependent deacetylase SIRT1, phenocopying aspects of SIRT1 deacetylase activation on mitochondrial metabolism (Bai et al. 2011). Thus, PARP provides a link between DNA damage and energy metabolism through direct effects on energy currencies as well as indirect effects of NAD+ and ATP dependent enzymes.

5. Conclusions

Cellular energy metabolism is a major source of ROS that can damage cellular components, including DNA. Oxidative DNA damage can in turn activate the DDR, a network of repair and signaling activities required for damage removal and stress adaptation. Inborn errors in DNA damage repair and signaling in human syndromes and mouse models typically display pathologies consistent with perturbation of growth and energy metabolism, including dwarfism and changes in insulin signaling and lipid accumulation. Interestingly, some disorders present with phenotypes reminiscent of the maladaptive response to nutrient/energy excess seen in metabolic syndrome. For example, in in A-T and Werner syndrome, these symptoms include dyslipidemia and insulin resistance. In other disorders, including mouse models of CS and TTD, symptoms appear on the opposite end of the nutrient/energy spectrum, with hypoglycemia, increased insulin sensitivity and reduced

adiposity reminiscent of the beneficial adaptations to DR. Over time, however, chronic activation of adaptations such as reduced IGF-1 that may be beneficial in the context of a wildtype mammal on a restricted diet may in fact become maladaptive in the context of genome instability. For example, mouse models of severe NER progeria have reduced IGF-1, but nonetheless have shortened lifespans, while restoration of IGF-1 levels in a mouse model of HGPS ameliorates disease symptoms. On the cellular level, recent data suggest that proteins involved in the DNA damage response can exert both direct and indirect control over pathways involved in energy metabolism and substrate utilization, including insulin and IGF-1 signaling. Which of these genetic defects leads to constitutive alterations in metabolic processes and which to adaptive responses to genotoxic stress remains to be fully elucidated. Furthermore, to what degree unrepaired DNA damage itself serves as the trigger for metabolic changes, and the identity of the causative lesion, is in most cases unknown. In conclusion, despite recent emerging data on a connection between the DNA damage response and energy metabolism, there is a relative dearth of studies on cellular or organismal energy metabolism in the context of genome instability disorders, with much remaining to be done in this burgeoning field.

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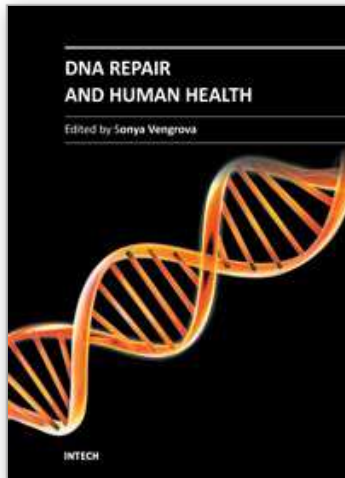
DNA Repair and Human Health

Edited by Dr. Sonya Vengrova

Over the past decades, great advances have been made in understanding the cellular DNA repair pathways. At the same time, a wealth of descriptive knowledge of human diseases has been accumulated. Now, the basic research of the mechanisms of DNA repair is merging with clinical research, placing the action of the DNA repair pathways in the context of the whole organism. Such integrative approach enables understanding of the disease mechanisms and is invaluable in improving diagnostics and prevention, as well as designing better therapies. This book highlights the central role of DNA repair in human health and well-being. The reviews presented here, contain detailed descriptions of DNA repair pathways, as well as analysis of a large body of evidence addressing links between DNA damage repair and human health. They will be of interest to a broad audience, from molecular biologists working on DNA repair in any model system, to medical researchers.

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