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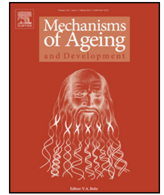

Cockayne syndrome pathogenesis: Lessons from mouse models

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ABSTRACT

Cockayne syndrome (CS) is a rare multisystem disorder characterized by cachectic dwarfism, nervous system abnormalities and features of premature aging. CS symptoms are associated with mutations in 5 genes, *CSA*, *CSB*, *XPB*, *XPD* and *XPG* encoding for proteins involved in the transcription-coupled subpathway of nucleotide excision DNA repair (NER). Mutant mice have been generated for all CS-associated genes and provide tools to examine how the cellular defects translate into CS symptoms. Mice deficient for *Csa* or *Csb* genetically mimic CS in man, and develop mild CS symptoms including reduced fat tissue, photoreceptor cell loss, and mild, but characteristic, nervous system pathology. These mild CS models are converted into severe CS models with short life span, progressive nervous system degeneration and cachectic dwarfism after simultaneous complete inactivation of global genome NER. A spectrum of mild-to-severe CS-like symptoms occurs in *Xpb*, *Xpd*, and *Xpg* mice that genetically mimic patients with a disorder that combines CS symptoms with another NER syndrome, xeroderma pigmentosum. In conclusion, CS mouse models mice develop a range of CS phenotypes and open promising perspectives for testing interventional approaches.

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1. Introduction

Cockayne syndrome (CS) is a rare autosomal recessive, multisystem disorder characterized by hypersensitivity to sun (UV) light, severe growth failure and cachexia (also termed cachectic dwarfism), short life span and progressive nervous system abnormalities. Symptoms include a characteristic aged facial appearance with protruding nose and sunken eyes (designated bird-like face) and thin hair, musculoskeletal abnormalities (contractures, kyphosis), progressive neurological and cognitive dysfunction, sensory-neural hearing loss and eye abnormalities (congenital cataract, retinal degeneration). The clinical presentation of CS varies and patients have been grossly divided into subgroups based on age of first symptoms and severity: Type II is characterized by prenatal onset, short lifespan (2–7 years), very small body size, and very severe neurological deficits (inability to sit, severe mental retardation); the moderate Type I (or classical form) of CS manifests symptom onset in the first two years after birth; the mild type III class displays juvenile or adult onset, life expectancies up to 40 years or later, and preserved ability to speak and walk (Laugel, 2013; Laugel et al., 2010; Nance and Berry, 1992; Natale, 2011). Although UV-sensitivity is a common feature of CS, the severity of this symptom does not necessarily correlate with most other symptoms. Problems related to sufficient food intake are a major clinical concern. The cause of death in most patients is pulmonary problems or kidney failure (Laugel, 2013; Natale, 2011).

A diagnostic feature of CS is impaired recovery of RNA synthesis in fibroblasts from patients after UV irradiation (Nakazawa et al., 2010). This defect results from deficiency in the transcription-coupled sub-pathway of nucleotide excision repair (NER). NER is a multi-step DNA repair pathway for removal of UV-induced DNA damage and a range of other helix-distorting lesions, in which the damage is excised as part of a 25–30 nucleotide single-strand fragment followed by gap-filling resynthesis and sealing of the remaining nick by ligation (Friedberg et al., 2006; Hanawalt and Spivak, 2008; Hoeijmakers, 2009). Transcription-coupled NER (TC-NER) specifically targets lesions in the template strand of active genes that block elongating RNA polymerase to allow rapid recovery of transcription (Fousteri and Mullenders, 2008; Hanawalt and Spivak, 2008). The complementary NER subpathway, termed global genome NER (GG-NER), differs in the initial damage recognition step, and removes helix-distorting DNA damage throughout the genome. GG-NER, which can be measured by UV damage-induced, non-S phase DNA repair synthesis (termed unscheduled DNA synthesis, UDS (Nakazawa et al., 2010)), is unaltered in CS, but is deficient in xeroderma pigmentosum (XP). XP is another rare recessive genetic photosensitivity syndrome

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characterized by sun-induced pigmentation abnormalities, a >1000 fold increased skin cancer risk, and in some patients accelerated neurodegeneration but in contrast to CS largely normal development (Khan et al., 2009; Soufir et al., 2010). In contrast to XP, CS patients do not show cancer predisposition, implying that TC-NER is not required for preventing cancer (Hoeijmakers, 2009).

CS is caused by recessive mutations in two genes, *CSA* (*ERCC8*) and *CSB* (*ERCC6*) (Laugel, 2013; Laugel et al., 2010). CSB is a DNA-dependent ATPase of the SWI2/SNF2 family that binds to lesion-stalled RNA polymerase II (RNA-Pol II) and recruits preincision NER factors (Fousteri et al., 2006; Lake and Fan, 2013; Lake et al., 2010). CSA is a 44 kDa WD-repeat-containing scaffold protein that assembles in a Cullin4-DDB1-RING ubiquitin ligase complex, termed CRL4CSA (Fischer et al., 2011). CSA determines substrate specificity of the complex with CSB as one of its potential clients (Fousteri and Mullenders, 2008; Groisman et al., 2006). CSA, like CSB, binds to lesion-stalled RNA-Pol II and is important for the recruitment of several factors including HMGN1, XAB2, TFIIS, and UVSSA (Fischer et al., 2011; Fousteri et al., 2006; Nouspikel, 2011; Zhang et al., 2012). Mutations in the *CSA* gene are generally associated with moderate (type I) and mild (type III) forms of CS, while mutation in the *CSB* gene cover the whole spectrum of CS phenotypes, including prenatal onset forms of CS (type II), and a severe variant termed COFS (cerebro-oculo-facio-skeletal-syndrome) that is characterized by different dysmorphic facial features (microcephaly, small deep-set eyes, prominent nasal root, and large ear pinnae), severe nervous system abnormalities, and absence of the cachectic appearance typical of CS (Jaakkola et al., 2010; Laugel et al., 2008; Meira et al., 2000).

The *CSA* and *CSB* mutations result in severe TC-NER dysfunction, but it has become clear that most of the CS symptoms cannot be explained by the sole loss of TC-NER function. First, XP-A patients, which harbor a complete combined GG-NER/TC-NER deficiency resulting from mutations in the gene encoding the core NER protein XPA, do not develop cachectic dwarfism and other typical CS symptoms, but develop XP, albeit usually in combination with progressive neurological abnormalities (Anttinen et al., 2008; DiGiovanna and Kraemer, 2012; Mimaki et al., 1986). Second, a small number of patients carrying a *CSA* or *CSB* mutation that causes severe TC-NER deficiency, do not develop CS, but develop UV-sensitive syndrome (UVSS), a rare photosensitivity disorder characterized by skin UV hypersensitivity as the only abnormality (Horibata et al., 2004; Nardo et al., 2009). Also mutations in the *UVSSA* gene, which recently have been identified as another cause of UVSS, result in severe TC-NER deficiency in the absence of CS symptoms (Nakazawa et al., 2012; Schwertman et al., 2012; Zhang et al., 2012). Importantly, cells from CS patients and mouse models, unlike UVSS and XP-A cells, display increased vulnerability to inducers of oxidative DNA damage (D'Errico et al., 2007; de Boer et al., 2002; de Waard et al., 2003; Gorgels et al., 2007; Nardo et al., 2009; Spivak and Hanawalt, 2006). These data indicate that the differences between symptoms in CS and UVSS may be explained by a differential vulnerability to different types of DNA damage, and that CSA and CSB are implicated in the removal of oxidative DNA lesions via a mechanism that does not require the whole NER machinery (Nakazawa et al., 2012; Nardo et al., 2009; Schwertman et al., 2012; Zhang et al., 2012). Accordingly, a recent live-cell imaging study revealed a rapid and transcription-dependent recruitment of CSB to sites of oxidative DNA lesions in the absence of detectable accumulation of downstream NER factors (Menoni et al., 2012). The term transcription-coupled repair (TCR) has been used to incorporate these broader, yet poorly defined XPA and UVSSA-independent protective activities (Hanawalt and Spivak, 2008; Hoeijmakers, 2009). In addition, it has been proposed that CS symptoms may follow from DNA damage in mitochondria (Kamenisch et al., 2010; Scheibye-Knudsen et al., 2012), or from transcriptional abnormalities independent of, or in complement to DNA repair deficits (Nouspikel, 2008).

CS symptoms also occur in a subset of XP patients that develop a combined XP/CS disorder caused by specific mutations in the *XPB (ERCC3)*, *XPD (ERCC2)* or *XPG (ERCC5)* genes (Oh et al., 2006; Scharer, 2008; Theron et al., 2005). XPB and XPD are helicases with opposite polarity (3′–5′ and 5′–3′, respectively) that are incorporated in the transcription/repair factor TFIIH. TFIIH performs opening and unwinding of DNA in GG-NER, TC-NER and transcription initiation by RNA-Pol I and RNA-Pol II (Fuss and Tainer, 2011; Hoogstraten et al., 2008). In NER, TFIIH also may be important for damage verification and positioning of the NER endonucleases, i.e. the ERCC1/XPF complex and XPG, that incise the damaged strand at the 5′ and 3′ sides, respectively. TFIIH consists of a heptameric ring-like core that contains XPB and XPD, and a trimeric dynamically associated complex: the Cdk-activating kinase (CAK) complex that is important in phosphorylation of the carboxy-terminal repeat-containing domain of RNA-Pol II. The CAK complex is released from the core during NER, and has additional TFIIH-independent functions (Compe and Egly, 2012; Fuss and Tainer, 2011). XPB and XPD are both essential for cell survival (Andressoo et al., 2009; de Boer et al., 1998b), but have differential roles in NER and transcription initiation: the helicase activity of XPB is essential for transcription, while XPD helicase activity is not. NER on the other hand depends on the helicase activity of XPD and the ATPase (but not helicase) activity of XPB (Compe and Egly, 2012; Fuss and Tainer, 2011).

Mutations in *XPB* and *XPD*, in addition to XP and XP/CS, can also cause trichothiodystrophy (TTD), a rare disorder that is defined by sulphur-deficient brittle hair and nails and fish-like skin (ichthyosis), but additionally incorporates a variable spectrum of other abnormalities. These include many features resembling CS: progressive neurodevelopmental deficits, severe growth deficiency, facial dysmorphisms, skeletal abnormalities, proneness to infections, and strongly reduced life expectancy (Faghri et al., 2008; Stefanini et al., 2010). TTD is regarded as a combined transcription-repair disorder resulting in part from reduced stability of the TFIIH complex, causing exhaustion of TFIIH and therefore transcriptional insufficiency before terminal differentiation of keratinocytes is completed. This leads to the TTD-specific brittle (unfinished) hair and nails and a scaly skin (Stefanini et al., 2010; Vermeulen et al., 2001). Reduced stability of the TFIIH in TTD is also suggested by the fact that in a subset of patients the disease is caused by mutations in *TTDA*, a small stabilizing subunit of the TFIIH core complex (Stefanini et al., 2010; Vermeulen et al., 2000). *TTDA* mutations although causing more than 70% loss of NER function and UV-sensitivity, do not cause prominent XP or CS symptoms (Stefanini et al., 2010).

XPG is the NER endonuclease that cuts at the 3′ site of the lesion (Fagbemi et al., 2011; Scharer, 2008). Mutations that selectively disrupt this nuclease activity cause 'pure' XP (without CS symptoms). Instead, XP/CS symptoms are associated with alleles that result in unstable or C-terminal truncated proteins (Emmert et al., 2002; Moriwaki et al., 2012; Scharer, 2008; Vermeulen et al., 1993). XPG has been assigned additional functions in transcription regulation, transcription-coupled repair and base-excision repair, independent of its endonuclease function, and these additional functions appear to depend on its C-terminus, which contains interaction sites with several proteins, including CSB and TFIIH (Ito et al., 2007; Lee et al., 2002; Sarker et al., 2005; Scharer, 2008; Shiomi et al., 2005; Thorel et al., 2004; Trego et al., 2011). Significantly, cells derived from XP-G XP/CS patients, like cells from CS-A and CS-B patients, but unlike cells from 'pure' XP XP-G patients, display increased sensitivity to inducers of oxidative DNA damage, further suggesting that inability to appropriately cope

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