Understanding photodermatoses associated with defective DNA repair

Photosensitive syndromes without associated cancer predisposition

Yik Weng Yew, MBBS, MPH,[a] Cerrene N. Giordano, MD,[b] Graciela Spivak, PhD,[c] and Henry W. Lim, MD[b]
Singapore; Detroit, Michigan; and Stanford, California

Learning objectives
After completing this learning activity, the participant should be able to describe the basic structure of the nucleotide excision repair pathways and the genes involved; compare and contrast photosensitive genodermatoses; and identify the genes and their protein products that become mutated/malfunctioning leading to the development of photosensitive syndromes.

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Photodermatoses associated with defective DNA repair are a group of photosensitive hereditary skin disorders. In this review, we focus on diseases and syndromes with defective nucleotide excision repair that are not accompanied by an increased risk of cutaneous malignancies despite having photosensitivity. Specifically, the gene mutations and transcription defects, epidemiology, and clinical features of Cockayne syndrome, cerebro-oculo-facial-skeletal syndrome, ultraviolet-sensitive syndrome, and trichothiodystrophy will be discussed. These conditions may also have other extracutaneous involvement affecting the neurologic system and growth and development. Rigorous photoprotection remains an important component of the management of these inherited DNA repair–deficiency photodermatoses. (J Am Acad Dermatol 2016;75:873-82.)

Key words: cerebro-oculo-facial-skeletal syndrome; Cockayne syndrome; nucleotide excision repair; photodermatoses; photosensitivity; trichothiodystrophy; UV-sensitive syndrome.

The diseases described in this article differ from xeroderma pigmentosum (XP) and other diseases discussed in the first article in this series in that the patients, while photosensitive, are not abnormally cancer-prone (Table I). Affected individuals may have severe developmental and neurologic defects that are distinct from those observed in patients with XP.[1]

TRANSCRIPTION-COUPLED REPAIR

Key points

- **Defects in the transcription-coupled repair pathway can result in diseases with photosensitivity, but these patients are generally not cancer-prone**
- **The transcription-coupled repair mechanism detects any adducts that disrupt the**

From the Department of Dermatology,[a] National Skin Centre, Singapore; Department of Dermatology,[b] Henry Ford Hospital, Detroit; and the Department of Biology,[c] Stanford University, Stanford.
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Correspondence to: Henry W. Lim, MD, Department of Dermatology, Henry Ford Hospital, 3031 W Grand Blvd, Ste 800, Detroit, MI 48202. E-mail: hlim1@hfhs.org.

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Abbreviations used:

6-4PP:	(6-4) pyrimidine-pyrimidone photoproduct
COFS:	cerebro-oculo-facio-skeletal
CS:	Cockayne syndrome
CPD:	cyclobutane pyrimidine dimer
ERCC:	excision repair cross-complementing
NER:	nucleotide excision repair
RNAP:	RNA polymerase
TCR:	transcription-coupled repair
TFIIS:	transcription factor IIS
TTD:	trichothiodystrophy
UV:	ultraviolet
$UV^{S}S$:	ultraviolet-sensitive syndrome
XP:	xeroderma pigmentosum

progression of RNA polymerases, activating protein complexes and transcription factors to bring about repair of the defects

- **Blocked RNA polymerase II constitutes the first step for damage recognition in the transcription-coupled repair pathway**
- **An arrested RNA polymerase II may be targeted for degradation; alternately, it may bypass the lesion with possible misincorporation of ribonucleotides, a phenomenon termed transcriptional mutagenesis**

In the process of RNA synthesis, a translocating RNA polymerase (RNAP) can be blocked by bulky adducts, such as the photoadducts cyclobutane pyrimidine dimers (CPDs) and 6-4 pyrimidine-pyrimidones (6-4PPs), cis-platin intrastrand cross-links, benzo[a]pyrene diol epoxide, and other polycyclic aromatic hydrocarbons; by discontinuities in the template strand (eg, nicks, gaps, and abasic sites); and by collisions with replication complexes. These complexes or defects can obstruct important metabolic processes, such as DNA replication; in mammals, they constitute a strong signal for apoptosis. Transcription-coupled repair (TCR) is a specialized mechanism for the detection and rapid removal of lesions that impede the progression of RNAP.

Blocked RNAPII constitutes the first step for damage recognition in TCR (Fig 1, *A*); there is no evidence to date for participation of human RNAPI, RNAPIII, or mitochondrial RNAP in TCR.[2,3] The arrested elongation complex recruits Cockayne syndrome B (CSB; also known as excision repair cross-complementing group 6 [ERCC6]), a transcription elongation factor that translocates along template DNA with RNAPII.[4] *CSB* recruits the *CSA* (*ERCC8*) complex, nucleotide excision repair (NER) factors, and chromatin remodeling factors, such as p300 and high mobility group nucleosome binding domain 1, to sites of arrested RNAPII, and has been considered the master coordinator of TCR in humans.

There are several potential outcomes after RNAPII arrest. An arrested RNAPII may be targeted for degradation through neural precursor cell–expressed developmentally downregulated protein 4 (Nedd4)-dependent ubiquitination and proteosomal degradation (Fig 1, *B*). Alternately, an arrested RNAPII may bypass the lesion with possible misincorporation of ribonucleotides, a phenomenon termed transcriptional mutagenesis[5] (Fig 1, *C*). Another proposed model is that the RNAPII reverses translocation with cleavage of the nascent transcript, also called backtracking, to reveal the offending lesion and to allow space for the repair complex to operate (Fig 1, *D*). Transcription factor IIS (TFIIS), a transcription elongation factor that stimulates mRNA cleavage by RNAPII, is recruited to sites of damage by CSA.[6] Lastly, TCR might be initiated by remodeling the RNAPII without removal from the arrest site[7] (Fig 1, *E*). Several protein complexes involved in chromatin remodeling, biogenesis of mRNA, and its export to the cytoplasm also participate in TCR (Table II).[8]

DISEASES WITH DEFECTIVE TRANCRIPTION-COUPLED REPAIR

Cockayne syndrome

Key points

- **Cockayne syndrome is a rare autosomal recessive disorder**
- **It comprises mainly 2 principal complementation groups, with mutations in the genes encoding Cockayne syndrome A and Cockayne syndrome B proteins (excision repair cross-complementing groups 8 and 6, respectively)**
- **Cells from patients with Cockayne syndrome are defective in the transcription-coupled repair subpathway of nucleotide excision repair**
- **Patients with Cockayne syndrome present with 3 major characteristics: microcephaly, stunted growth, and progressive neurologic dysfunction caused by leukodystrophy**
- **Cutaneous manifestations include photosensitivity, dry thin skin, dry hair, anhidrosis, and acral cyanotic livedo**
- **Patients do not develop sun-induced pigmentation and are not prone to ultraviolet light–related skin malignancies**

Background. Cockayne syndrome (CS) is a complex disease with a multitude of symptoms.