Mutation Research 776 (2015) 24–30

Contents lists available at ScienceDirect

Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis

journal homepage: www.elsevier.com/locate/molmut
Community address: www.elsevier.com/locate/mutres

Review

Photosensitive human syndromes

Graciela Spivak*, Philip C. Hanawalt

Department of Biology, Stanford University, Stanford, CA 94305, USA

ARTICLE INFO

Article history:
Received 14 July 2014
Received in revised form 17 October 2014
Accepted 6 November 2014
Available online 14 November 2014

Keywords:
Photosensitivity
DNA repair
Skin cancer
Global genomic repair
Transcription-coupled repair

ABSTRACT

Photosensitivity in humans can result from defects in repair of light-induced DNA lesions, from photoactivation of chemicals (including certain medications) with sunlight to produce toxic mediators, and by immune reactions to sunlight exposures. Deficiencies in DNA repair and the processing of damaged DNA during replication and transcription may result in mutations and genomic instability. We will review current understanding of photosensitivity to short wavelength ultraviolet light (UV) due to genetic defects in particular DNA repair pathways; deficiencies in some are characterized by an extremely high incidence of cancer in sun-exposed tissues, while in others no cancers have been reported.

Contents

* Corresponding author at: Department of Biology, Stanford University, 385 Serra Mall, Stanford, CA 94305-5020, USA. Tel.: +1 650 723 2425; fax: +1 650 723 2425.
E-mail address: gspivak@stanford.edu (G. Spivak).

http://dx.doi.org/10.1016/j.mrfmmm.2014.11.003
0027-5107/

1. Introduction

Light emitted by the sun is essential for life on Earth. In particular, it is necessary for photosynthesis in plants and for the production of vitamin D in mammals. However, sunlight can also be harmful; in humans it causes aging of the skin and cancer, in addition to photodermatoses. Cellular biomolecules, particularly nucleic acids, sustain light-induced damage; the types of lesions depend upon the wavelengths to which the cells are exposed. Various strategies have evolved to reverse or remove the photoproducts in DNA that can interfere with vital functions such as replication and transcription. Essentially all living organisms (with the exception of placental mammals) produce highly effective photolyases that can directly reverse the principal sunlight-induced DNA lesions by the process known as photoreactivation. Otherwise, these photoproducts can be recognized and removed by the ubiquitous pathway of nucleotide excision repair (NER). NER operates in two modes, throughout the genome as global genomic repair (GGR), and on the transcribed strands of active genes as transcription-coupled repair (TCR) (reviewed in [1], Fig. 1).

UVC (100–280 nm) radiation from the sun is completely screened out by dioxygen and ozone in the upper atmosphere. UVB (280–315 nm) is greatly attenuated by the ozone layer, but the small fraction of these wavelengths that reach the earth's surface can affect all life forms. They induce damage to DNA and RNA by direct excitation, with a maximum quantum yield at ~260 nm. The primary products caused by these wavelengths are cyclobutane pyrimidine dimers (CPD) and (6-4) pyrimidine-pyrimidone photoproducts (6-4PP), which can form between adjacent pyrimidines in the DNA. Mutations in genes that code for factors involved in the repair of these photoproducts result in enhanced photosensitivity, manifested as acute sunburn, pigmentation anomalies, dryness and atrophy of the skin, and in some patients, a high incidence of cancer in sun-exposed areas.

Although UVA, in particular 340–400 nm radiation, can cause acute reactions in photosensitive patients, it was generally assumed that these wavelengths do not directly affect DNA; however recent studies using powerful analytical tools and effective filters have shown that CPD but not 6-4PP are generated by UVA [2]. Photosensitized reactions (e.g. with tryptophan in proteins) can result in the formation of reactive oxygen species (ROS) leading to oxidation of DNA bases, for example, 8-hydroxyguanine (8-oxo-7,8-dihydroguanine, 8-oxoG) [3,4]. There are currently no human syndromes for which sunlight sensitivity is caused by deficient repair of oxidized DNA bases. However, inhibition of the various steps in the base excision repair (BER) pathway causes cellular hypersensitivity to UVA [5], and laboratory mice with engineered mutations in genes coding for enzymes that initiate BER are somewhat prone to skin cancer upon exposure to UVB [6], but they are not generally sun-sensitive [7]. NER-deficient human cell lines have been reported to be hypersensitive to ROS [8,9]; however, mutation spectra analyses in skin tumors from patients defective in NER reveal that essentially all the mutations had been caused by CPD or 6-4PP [10].

Pathologies associated with visible light and radiations in the longer wavelength regions have been reported, albeit rarely; the roles of these wavelengths in skin disease, if any, are poorly understood.

By far, most of the hereditary photosensitive disorders involving DNA repair are due to NER deficiencies; exceptions for which the defects are known include Bloom's and Rothmund–Thompson syndromes and ataxia telangiectasia, as described below and listed in Table 1.

2. DNA repair and photosensitivity

2.1. Photosensitivity and defects in DNA helicases

Five homologs of the *recQ* gene from *Escherichia coli*, which codes for a DNA helicase with 3′–5′ directional specificity involved in recombination and repair of DNA breaks, have been identified in humans. In addition to Bloom's and Rothmund–Thomson syndromes, Werner's syndrome is also due to mutations in a RecQ-like helicase, the *WRN* (*RecQL2*) gene; although patients exhibit premature aging and early onset sarcomas and mesenchymal tumors, photosensitivity has not been reported. Mutations in the other two human RecQ-like helicases, RECQL1 and RECQL5, have not yet been genetically linked to a disease [11].

2.1.1. Bloom's syndrome

Bloom's syndrome is a rare chromosome breakage disease primarily seen among Ashkenazi Jews. It presents with failure to thrive, stunted growth, small and narrow facies, sun-sensitive facial telangiectasias, immunodeficiency, and increased risk of malignancies. Mutations in the *BLM* gene, which codes for the RecQL3 (BLM) DNA helicase, are associated with the syndrome. Cells from Bloom's syndrome patients exhibit high frequencies of sister chromatid exchanges, chromosome aberrations and rearrangements, reflecting the high mutation rate associated with the loss of BLM [12].

2.1.2. Rothmund–Thomson syndrome (RTS)

Rothmund–Thomson syndrome (RTS) or poikiloderma congenitale, is a rare autosomal recessive disorder attributed to mutations in the *RECQL4* helicase gene. Key features include early photosensitivity and poikilodermatous (abnormal pigmentation) skin changes, juvenile cataracts, skeletal dysplasias, and a predisposition to osteosarcoma and skin cancer. The acute phase of the disease appears in early infancy as red patches on the cheeks, spreading later to other areas of the face, extremities or buttocks. Roughly 30% of the patients are photosensitive [13]. Individuals with mutations in *RECQL4* can also develop RAPADILINO, a disease very similar to RTS, but without photosensitivity and poikiloderma [14].

2.2. Photosensitivity due to defects in DNA damage response pathways

2.2.1. Ataxia telangiectasia (AT)

Ataxia telangiectasia (AT) also known as Louis–Bar syndrome, results in ataxia (lack of muscle control), immune deficiency, elevated cancer incidence, and premature aging. This autosomal recessive disease is caused by mutations in the *ATM* gene, a key factor in the cellular response to DNA damage, particularly double-strand breaks. Moreover, *ATM* regulates telomere length, and this might correlate with the progeria observed in most patients. Although AT patients are not photosensitive, telangiectasia due to broken venous capillaries usually appears in childhood several years following ataxia, and this is more evident in sun-exposed areas of the skin, although sun-protected areas such as the flexural surfaces of the extremities and the chest are also typically affected. Other common cutaneous findings that contribute to the progeroid appearance include atrophy of subcutaneous fat and graying hairs.

2.3. Photosensitivity and defects in NER

The spectrum of human disorders resulting from mutations in NER proteins has been presented in a number of recent reviews, including [15–18]. Here we will summarize the major characteristics of each of these diseases.