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REVIEW PAPER

Ultraviolet radiation: DNA damage, repair, and human disorders

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Abstract Ultraviolet (UV) radiation is one of the most common environmental health hazards that cause highly toxic effects in most living organisms. UV irradiation leads to harmful effects including skin aging, eye damage, and skin cancer because of increased production of cellular reactive oxygen species and by direct DNA damage. Damaged DNA, if not properly repaired, is a source of mutation, and interferes with many cellular mechanisms such as replication, transcription, and the cell cycle. Because most UV damaged DNA is efficiently repaired by nucleotide excision repair (NER), which is a specialized UV-induced DNA damage repair system, many UV-induced symptoms are closely related to NER. Therefore, understanding the function of NER genes will elucidate the cause of different UV-induced symptoms. Furthermore, a multidisciplinary understanding of damaged DNA repair systems and other cellular mechanisms affected by unrepaired DNA damage would lead to an improved understanding of UV-induced symptoms and toward developing various preventive and therapeutic methods against UV damage. For this purpose, in this review we discuss two NER-related human genetic disorders, xeroderma pigmentosum (XP) and Cockayne syndrome (CS), the cellular mechanisms that are impaired by defective NER genes, and the functions of *RAD2/XPG* in relation to the cause of various UV damage-induced symptoms.

Keywords: UV, NER, XP, CS, RAD2/XPG, Actin dynamics

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Exposure to harmful environmental factors causes various cellular responses including DNA damage, cell death, cancer, and aging. Among those environmental factors, UV radiation from sunlight is the most common environmental health hazard that most living organisms are exposed to on a daily basis. UV radiation has wavelengths shorter than visible light (700-400 nm) and is classified as UVA (315-400 nm), UVB (290-315 nm), and UVC (280-100 nm). Most UVC is absorbed by the ozone layer, and only UVA and UVB compose ground level UV radiation[1,2]. Both UVA and UVB are blamed for premature skin aging, eye damage, and skin cancer although UVB has a beneficial effect by playing an important role in vitamin D formation[1,3]. Serious harmful effects of UV irradiation are largely due to DNA damage by UVA and UVB. UV damages cellular DNA indirectly by producing reactive oxygen species, and directly by covalent modification of neighboring pyrimidines[1,2]. Cyclobutane pyrimidine dimers and 6-4 photo products are two major UV-induced DNA lesions[1]. Since UV-induced DNA damage causes genetic alterations that result in mutagenesis and cancer formation, such damaged DNA must be repaired or removed to maintain genetic integrity. Most UV-damaged DNA is repaired by specialized UV-damaged DNA repair systems called NER. Although NER system effectively removes damaged-DNA, accumulation of DNA damage by excessive UV exposure could surpass repair capacity which leads to persistent DNA damages resulting in mutations, cell death, cancer and aging. In fact, mutations in NER-related genes cause genetic disorders associated with cancer, such as XP, and/or premature aging, such as CS because of insufficient repair of damaged DNA.

Unrepaired damaged DNA as the source of mutation is supported by increased incidence of skin cancer and skin aging in patients with NER deficiencies; however, UV-induced mutations are not sufficient to account for all extended UV-exposure-induced symptoms such as

sun burn, immune system suppression, skin cancer, skin aging, photokeratitis, melanoma within the eye, corneal damage, macular degeneration, and cataracts. In fact, UV-induced DNA damage would impair different cellular mechanisms, such as transcription, replication, and other cellular processes[4]. The outcome depends on the mechanism affected by damaged DNA. For example, UV-induced skin cancer and skin aging are contradictory phenomena that are caused by failure of different cellular functions. Because most UV DNA damage is repaired by NER, many UV-induced symptoms are closely related to the NER system. Therefore, findings on the functions of NER-related genes provide clues for the cause of UV-induced symptoms. Recent reports on the causes of XP or CS (described later in this review) found that some NER genes have multiple functions that are turned on or off depending on the degree of DNA damage or environmental conditions. Therefore, predictions of the outcome would be different depending on how the respective process was affected during and after UV DNA damage repair. For instance, *RAD2*, which is a yeast NER gene, was first identified as an endonuclease, but was found to function in transcription elongation[5], cell cycle regulation[6], and regulation of actin dynamics[7]. This multifunctional capacity of NER-gene is further illustrated by two different genetic disorders caused by different mutations in the same gene. For example, the location and type of mutation in *XPG*, which is the human homolog of *RAD2*, causes either XP or CS with differing severity of symptoms. Thus, studying the underlying mechanisms of XP/CS is valuable because it could broaden our knowledge about the effects of DNA damage in many cellular mechanisms.

UV radiation is an increasing environmental problem, in particular, due to the destruction of the ozone layer, which filters all UVC and most UVB. Destruction of the ozone layer results in increased amounts of UV radiation and UV-induced disorders including skin cancer[1,8]. Therefore, research on UV-induced DNA damage repair not only provides an understanding of the pathway, but also furthers our understanding regarding treatment and protection against UV-induced DNA damage. To understand the effects of UV-induced DNA damage, this review article will discuss, 1) the NER, a UV DNA damage repair system, 2) the genetic disorders XP and CS, which are caused by mutations in NER-related genes, 3) the newly discovered regulatory functions of *RAD2*, a yeast homolog of human *XPG*, in actin dynamics 4) implications of the findings on the cause of XPG/CS in relation to symptoms found in patients with CS, and 5) future perspectives.

NER, XP, and CS

Over 30 proteins are involved in NER. Following recognition of UV-induced DNA damage, the DNA helix is unwound, and the flanking 3′- and 5′-sides of the lesion are cleaved by two NER endonucleases XPG and ERCC1-XPF, respectively. Next, the damaged-DNA containing nucleotide is excised followed by re-synthesis of the gaps[9,10]. NER is a very efficient repair system; however, prolonged UV exposure can cause accumulation of UV-induced DNA damage, leading to cell death, accelerated skin aging, and increased risk of skin cancer[11].

Mutations in certain NER-related genes in humans cause XP, which is an autosomal recessive genetic disorder, characterized by increased UV sensitivity, a characteristic pigmentation in sun-exposed skin, and a dramatically increased incidence of skin cancer by more than thousand-folds[12-14]. XP is classified into eight complementation groups from XPA to G and the variant group XPV. Each complementation group is associated with mutations in a specific NER-related gene, namely XPA through XPG, and XPV, respectively (Table 1)[12,14]. On the other hand, mutations in three XP genes (*XPB*, *XPD*, and *XPG*) and two other NER-related genes (*CSA*, and *CSB*) cause CS that is characterized by retarded somatic and brain growth, impaired neurological development, mental retardation, and premature aging (Table 2). Patients with CS exhibit sun sensitivity and various indicators of physiological and senile aging including gradual neuronal

Table 1. Xeroderma pigmentosum complementation groups and genes.

Group	Gene	Yeast homolog	Protein function
XP-A	*XPA*	*RAD14*	damage recognition
XP-B	*XPB*	*RAD25*	helicase, a component of TFIIH
XP-C	*XPC*	*RAD4*	damage recognition
XP-D	*XPD*	*RAD3*	helicase, a component of TFIIH
XP-E	*XPE*		damage recognition
XP-F	*XPF*	*RAD1*	endonuclease, 5′ incision
XP-G	*XPG*	*RAD2*	endonuclease, 3′ incision
XP-V	*POLH*	*RAD30*	DNA polymerase

Table 2. Premature aging syndromes.

Syndrome	Gene	Protein function	Defect
Werner syndrome	*RECQL2/WRN*	DNA helicase	genomic instability, cancer predisposition
Bloom syndrome	*RECQL3/BLM*	DNA helicase	genomic instability, cancer predisposition
Rothmund-Thomson syndrome	*RECQL4*	DNA helicase	genomic instability, cancer predisposition
Ataxia Telangiectasis	*ATM*	Serine/threonine protein kinase	genomic instability, cancer predisposition
Hutchinson-Gilford syndrome	*LMNA*	Nuclear architecture	chromatin disorganization, DNA damage increase
Trichothiodystrophy	*XPB* *XPD* *P8/TTDA*	DNA helicase, TFIIH subunit DNA helicase, TFIIH subunit TFIIH subunit	genomic instability, DNA repair defect
Cockayne syndrome	*CSA* *CSB* *XPB* *XPD* *XPG*	TC-NER TC-NER DNA helicase TFIIH subunit DNA helicase TFIIH subunit endonuclease	genomic instability, transcription defect, DNA repair defect, actin dynamics defect, cell cycle defect

degeneration, and hearing and visual impairments[15,16]. Notably, the mean lifespan of patients with CS is approximately 12.5 years[17-19].

Although the causative genes of both XP and CS are involved in NER, these two disorders exhibit substantially different characteristics beyond certain common features. The most distinctive similarities between XP and CS are extreme sensitivity to UV irradiation and impaired DNA damage repair. However, the most distinctive differences between those two NER-related disorders are premature aging in patients with CS and cancer predisposition in patients with XP. Furthermore, premature aging is found only in patients with CS, whereas cancer incidence is increased greater than a thousand-fold in patients with XP while it is not increased in patients with CS[12-17,19].

Causes of CS

The natural aging process is defined as the accumulation of changes in an organism throughout its lifetime, whereas premature or accelerated aging is an unnatural aging process in which affected individuals appear older than their chronological age[20]. Excessive exposure to UV, can accelerate skin aging[1,2], and genetic alterations of some genes cause premature aging syndromes. Features of individuals with premature aging syndromes include graying and loss of hair, wrinkling, soft tissue calcification, cardiovascular problems, impairments of vision and hearing, osteoporosis, diabetes mellitus, and cancers. Inherited syndromes characterized by rapid aging and shortened lifespan are called progeroid syndromes, which are predominantly found in groups with genetic disorders, including Werner syndrome (WS), Bloom syndrome, CS, trichothiodystrophy (TTD), Rothmund-Thomson syndrome, ataxia talangiectasis, and Hutchinson-Gilford progeria syndrome[10,12,20,21]. Interestingly, the majority of known disorders of premature aging are associated with mutations in DNA repair-associated genes. Among those, CS is caused by mutations in specific NER-related genes (Table 2).

The products of the CS genes have various cellular functions related to transcription. CSA and CSB function in transcription initiation and elongation, and in transcription-coupled NER (TC-NER), which is a subpathway of NER responsible for faster removal of DNA damage on the transcribed strand[22,23]. In addition, XPB and XPD are components of TFIIH which functions in both transcription and NER[9]. In contrast, the role of XPG in transcription was not well understood until a study using yeast *rad2* mutants that suggested *XPG* had a role in transcription elongation[5]. This finding appeared to address the controversy whether transcription was the elemental cause of CS. Now that is known all five CS-related genes have a role in transcription, CS is considered as a transcription disorder[9,24,25].

Nevertheless, the fundamental cause of CS remains controversial because some symptoms associated with the disorder cannot be accounted for by impaired transcription. In particular, the fact that there is no increase in cancer incidence in patients with CS compared to the greater than thousand fold increase found in patients with XP cannot be readily consolidated by de-

fects in transcription caused by of CS-related genes. Reid-Bayliss *et al*.[26] observed that cultured cells from patients with CS exhibited normal levels of mutagenesis despite possessing comparable sensitivity to UV in cells from patients with XP. The low UV-induced mutagenesis found in cells from patients with CS accounts for the lower incidence of cancer compared to that found in patients with in XP. However, the mechanism in which these cells exhibit lower mutagenesis has not been elucidated. Thus, how common symptoms of CS can arise from random transcription defects of various genes in different affected patients remains unknown. Moreover, XP/CS phenotypes are not manifested in some XPD C-terminal mutants in which transcription is impaired. In addition, defects of two TFIIH subunits, p44 and p52, destabilize TFIIH but do not cause any known human disease[24].

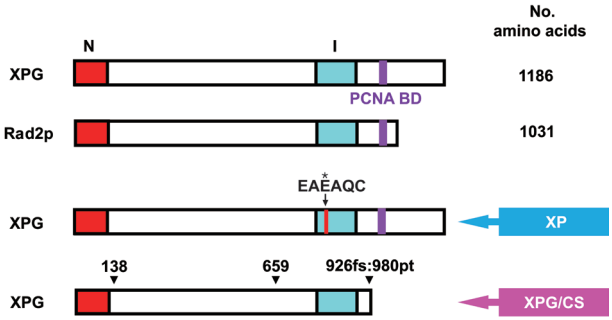

Figure 1. Schematic presentation of mutations in XPG protein. The E(*) residue in EAE(*)AQC sequence is corresponds to the E791 residue in XPG and the E794 residue in Rad2p. Arrowheads indicate the location of C-terminal truncation mutations in XPG cells isolated from the three patients with XPG/CS. N: N-terminal domain, I: Internal domain, fs: frame shift mutation, pt: protein termination.

XPG/RAD2

The functions of many NER-related genes and other genes involved in aging such as *TOR* and *SIRT* were initially discovered in yeast before the identical functions were revealed in higher eukaryotes including humans[27]. Baker's yeast, *Saccharomyces cerevisiae*, is a popular model organism for studying the function of genes in aging and accelerated aging disorders such as CS and WS[5-7,28]. Yeast possesses homologs of most human NER-related genes, and the functions of yeast homologs are highly conserved to their human counterparts. Despite being a unicellular eukaryotic cell, this organism has contributed greatly to broadening our understanding of the molecular functions of genes not only in yeast but also in higher eukaryotes including humans.

XPG/RAD2 has been the center of controversy regarding the fundamental cause of CS. *RAD2* is the yeast homolog of human *XPG* gene, and both Rad2 protein (Rad2p) and XPG which are essential endonucleases in the NER system, have two conserved regions at the N-terminus (N) and in the internal domain (I) (Figure 1). Impaired XPG endonuclease activity by point mutations in a conserved EAEAQC sequence in the I-region causes XP. In addition, the E791A mutation abolishes 3′-endonuclease activity of XPG and the mutant protein does not restore XPG activity in XPG mutant cells[29]. The yeast *rad2*E794A mutant that mimics the XPGE791A mutation exhibits a high UV sensitivity similar to that found in the XPGE791A cells[5]. Although 3′-incision of damaged DNA is the main function of XPG, there are evidences that it has additional roles.

Because XPG/CS is caused by the C-terminal deletion of XPG whereas mutations in the I-domain of XPG cause XP[30], the function of the XPG C-terminal region has been the target of significant researches to determine the cause of XPG/CS. In the 1990s, it was demonstrated that the C-terminal region of XPG interacted with proliferating cell nuclear antigen (PCNA) and participated in cellular localization, but that, the function of this interaction was not related to NER[31]. The role of the XPG-PCNA interaction remains unsolved. Furthermore, a lack of support between the XPG PCNA-binding domain (BD) and CS phenotypes were suggested in a study of mouse XPG deletion mutants. xpgΔex15 mice, which have a 183 amino acids deletion in the XPG C-terminal 183 amino acids that includes PCNA-BD, did not exhibit CS phenotypes, whereas xpgD811stop mice, in which C-terminal 360 amino acids of XPG were deleted, exhibited growth retardation and a shortened lifespan[32]. Recently, it was found that PCNA-BD in yeast Rad2p has a function in mutagenesis and cell-cycle regulation under UV-exposure condition[33]. However, the function of XPG/Rad2p PCNA-BD may be excluded as the cause of XPG/CS because deletion of XPG PCNA-BD did not cause CS[32].

XPG interacts with multiple partners through its C-terminal region[34]. In particular, it was found that the XPG C-terminal region has a role in stabilizing XPG-TFIIH complex formation[35], and that amino acids 747-928 are involved in the interaction between XPG and TFIIH components[36]. These findings may support that the functional failure of XPG in transcription causes of XPG/CS. However, the smallest XPG C-terminal deletion found in XPG/CS cells, which were derived from patient XPCS1RO is 258 amino acids (from amino acids 926 to 1186)[37]. These findings indicate that neither XPG-TFIIH nor XPG-PCNA interaction might be the cause of CS, but that the XPG C-terminal region, be-

tween amino acids 926 and N-terminal to the PCNA-BD, is responsible for XPG/CS (Figure 1).

RAD2 in cell cycle regulation

Kang *et al*.[6] found that overexpression of Rad2p causes cell growth arrest and mitotic catastrophe and that the C-terminal region of Rad2p was responsible for the observed effects. Based on these findings, it was proposed that a function of the Rad2p C-terminal region was coordination of cell cycle regulation and damaged DNA repair. Although this study of *RAD2* overexpression was performed in the absence of extrinsic DNA damage, Rad2p-induced cell cycle regulation may reflect its cellular role under DNA damaging conditions because *RAD2* expression is induced by UV exposure[38]. Furthermore, recent functional studies of Rad2p found unsuspected functions of Rad2p related to cell cycle regulation in the presence of UV damage[7,33].

To verify the function of the *XPG*/*RAD2* C-terminal region in the pathogenesis of CS, Kang *et al*.[7] analyzed various *rad2* C-terminal deletion (*rad2*CΔ) mutants, which mimic the *XPG* mutations found in patients with XPG/CS, in the presence of UV. They found that in the absence of UV exposure, *rad2*CΔ mutants did not exhibit any notable changes compared to wild type (WT). However, following UV irradiation, it was found that cell cycle and cell growth of *rad2*CΔ mutants were arrested. This finding indicates that the C-terminal region of Rad2p is responsible for the cell cycle regulation. Analysis of serial *rad2* C-terminal deletion mutants defined the specific sequences responsible for the CS-like phenotypes to those corresponding to the XPG C-terminal region between amino acid 926 and N-terminal to PCNA-BD.

DNA damaging agents induce genes that modulate cell cycle progression and repair DNA damage[39]. Following damaged DNA repair, re-initiation of cell cycle from DNA damage-induced cell cycle arrest is required to maintain viability and growth. Interestingly, some characteristic symptoms of CS such as retarded growth and premature aging arise from compromised cell cycle progression. In fact, impairments in cell cycle regulation are frequently observed in CS cells after damage-induced cell cycle arrest[40]. In addition, interruption of the cell cycle after DNA damage in CS cells may be a plausible explanation for the lack of an increased incidence of cancer in patients with CS. In other words, mechanisms other than transcription, and in particular, related to cell cycle regulation, may be the major cause of CS.

Actin cytoskeleton dynamics and XPG/CS

Investigation in the role of the *rad2* C-terminal region revealed that it is important for cell cycle regulation and regulation of cell polarization through actin dynamics after UV irradiation. Eukaryotic morphogenesis and development are determined by the structure of the actin cytoskeleton[41,42]. Compromised actin dynamics because of the C-terminal deletion of *rad2*, which mimics the shortest XPG C-terminal deletion reported in a patient with XPG/CS, indicates the XPG C-terminal region is required for re-initiation of the cell cycle from damage-induced cell cycle arrest.

The actin cytoskeleton largely functions in cell polarity. However, it has been demonstrated that the actin cytoskeleton participates in other cellular processes such as cell growth, survival, development, gene expression, morphogenesis, and cell cycle checkpoint control[41,43,44]. Furthermore, neurodegenerative disorders and mental retardation in humans are associated with defective actin cytoskeletal regulation[45,46]. Alzheimer's and Parkinson's disease, two well-known aging-related neurodegenerative diseases, are considered as the cytoskeleton related disorders[47]. Moreover, the most pronounced characteristics of CS are global growth and developmental failure accompanying profound neurodegeneration[15,16]. It has been unclear why certain tissues, specifically neuronal cells and muscle cells, are affected more in CS. Because a noticeable characteristic of CS is neurodegeneration, defective cytoskeletal dynamics are a plausible cause of CS as observed in the yeast *rad2*CΔ mutant[7]. Proper regulation of actin dynamics is essential for induction of skeletal muscle-specific genes and neuronal cell development[41,48]. Furthermore, dysmyelination and the consequent neurological symptoms observed in a mouse model of CS were similar to the reduction of oligodendrocytes and myelination found in brains of patients with CS[46].

Although evidences supports a connection between actin dynamics and CS symptoms, a role of XPG in the regulation of actin dynamics has not been investigated largely because of the lack of prior evidence for an association. Yeast studies of defective regulation of actin dynamics in the *rad2*CΔ mutant after UV exposure provide support for a connection between actin dynamics and CS symptoms[6,7]. Transiently increased expression of *RAD2* and *XPG* upon DNA damage[38,49], and the observation of unique morphological and cytoskeletal alterations after UV irradiation in the *rad2*CΔ mutant[7], indicates that XPG/Rad2p-associated cytoskeletal changes occur solely after DNA damage. The transient damage-induced XPG expression[49] indicates that regulation of actin dynamics by XPG in UV-damaged cells would be short-lived. Therefore, the effect of XPG on the actin cytoskeleton would not be observable in normal cells. However, similar to the yeast

*rad2*CΔ mutant after UV exposure, it is plausible that regulation of actin dynamics in cells containing the XPG C-terminal truncation mutation is delayed and actin regulation-related cellular mechanisms are deteriorated in the presence of UV irradiation. Examination of the role of XPG in the regulation of actin dynamics is important to verify whether XPG function is responsible for specific symptoms, such as neurodegeneration and muscle degeneration in patients with CS.

Future perspectives

Although UV has certain beneficial effects, such as vitamin D production, extended UV exposure causes various disorders, because of un-repaired damaged DNA or cellular pathways by DNA damage blockage. Because damaged DNA impairs replication, transcription, and the cell cycle, repairing or mitigating DNA damage is critical for maintaining cellular genetic integrity to prevent skin cancer and aging. Researches on the mechanisms of NER and the functions of related genes have significantly improved our understanding not only in damaged DNA repair but also in replication, transcription, cell cycle, cancer, and aging. Cellular responses to UV damage are multidirectional. In cases of XP and CS, two different genetic disorders caused by different mutations in the same genes, the effects of UV damage are markedly different. Cancer predisposition is extremely increased in patients with XP, but not in patients with CS. Taking advantage of the facts and current molecular research techniques, XP and CS mutant cells can be applied to isolate and develop targets for anti-UV therapeutics, cancer therapeutics, and anti-aging reagents. In addition, further study of factors that activate the NER system may provide new candidate compounds with UV protection effects.

Skin aging is stimulated by UV exposure, whereas premature aging syndromes are genetic disorders. However, CS is caused by mutations in particular genes and is associated with UV irradiation. Therefore, understanding CS as a premature aging syndrome is important for understanding the connection between UV DNA damage and premature aging. The cause of CS is not entirely understood although the condition has investigated for many decades. New insight in the function of *RAD2* in the cell cycle and regulation of actin dynamics imply hitherto unknown role of XPG in aging in the presence of DNA damage. The high structural and functional homology between XPG and Rad2p indicate that human XPG functions in the regulation of actin dynamics similar to that of Rad2p in the presence of UV damage. To demonstrate that XPG has the same function, studies on the regulation of actin dynamics of XPG in the presence of UV are required. Nonetheless, the regulation of actin dynamics by XPG may short-lived which would represent a significant technical challenge in studies of XPG function in the regulation of actin dynamics in human cells because XPG expression after UV-damage would be transient. In addition to identifying the function of XPG in the regulation of actin dynamics, determination of the role of other CS genes, such as *XPB*, *XPD*, *CSA*, and *CSB*, in the mechanism of regulating actin dynamics in the presence of UV are warranted. However, these genes may function co-operatively with XPG instead of singly in regulating actin dynamics. In addition to determining the effects of UV DNA damage in premature aging, studying the cause of premature aging symptoms of CS has broadened our knowledge of natural aging. Because premature aging mimics physiological aging in many ways, understanding the underlying mechanisms of premature aging can provide insights into the aging process as well as an improved understanding and, potentially, treatment of senile diseases.

"Omics" approaches have been widely used to collectively characterize and quantify biological molecules, which may be useful tools for identifying therapeutic and preventive targets against UV damage. Large scale comparisons of genes, proteins, and metabolites expressed in cells in the presence versus absence of UV exposure will provide information regarding the different pathways or cellular molecules for the diagnosis of cancer or aging, and novel targets for UV protection and UV damage therapy.

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