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Review

Histone Modifications Induced by Chemicals and Photogenotoxicity

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Photogenotoxicity is generally defined as the ability of chemicals to induce genotoxic effects under ultraviolet (UV) and/or visible light. The potential of chemically-induced epigenetic alterations in the nucleus to affect the genotoxicity of UV has been discussed in this review. UV induces the formation of pyrimidine dimers and is, therefore, considered to be genotoxic. Pyrimidine dimers are effectively repaired by nucleotide excision repair (NER), a process in which the relaxation of nucleosome interactions is considered necessary. Histone modifications such as acetylation are a cause of the change of nucleosome interactions, and previous studies and reviews demonstrated that these modifications altered the generation as well as repair of DNA damage. We previously reported that the hyperacetylation of histones enhanced sensitivity to UV light and suppressed NER. Some chemicals, metals, pesticides, and hormones have been shown to acetylate histone residues. The dysregulation of histone modifications caused by these chemicals may affect the formation of pyrimidine dimers following exposure to UV light as well as repair ability, which suggests the new concept of ''photogenotoxicity''.

Key words: histone, acetylation, nucleotide excision repair, pyrimidine dimers, photogenotoxicity, UV, chemicals

Introduction –Photogenotoxicity–

Photochemical genotoxicity or ''photogenotoxicity'' is defined as the ability of chemicals to induce genotoxic effects when irradiated with ultraviolet (UV) and/or visible light (Fig. 1A). The phototoxic effects observed following the absorption of light by chemicals have been divided into two types (1). Type I phototoxicity that chemicals acquiring an excited state after the absorption of light directly react with an important cell constituent or transfer electrons or hydrogen atoms. Type II is phototoxicity that chemicals adsorbing light go from an excited singlet state to a triplet state, and react with molecular oxygen to produce singlet oxygen, the superoxide anion, and hydrogen peroxide. Types I and II both induce DNA damage; therefore, assessing the photogenotoxic potentials of certain drugs and cosmetic products is important (2,3).

Other patterns of photogenotoxicity can be concidered (Fig. 1B and C). Chemicals that are exposed to UV and/or visible light are oxidized and degraded, which consequently changes their genotoxic potential (Fig. 1B). For example, the reactive intermediates of polycyclic aromatic hydrocarbons (PAHs) were found to be more genotoxic than parent PAHs following exposure to UV (4–6). Bezo[a]pyrene (BaP) did not phosphorylate histone H2AX, a marker for DNA double strand breaks (DSBs), whereas UV-exposed BaP significantly phosphorylated histone H2AX (4). BaP was degraded and some oxidized BaP, which may be genotoxic, were formed (6). Genotoxicity due to the photooxidation and photodegradation of chemicals needs to be examined in more detail.

UV in sunlight is also genotoxic in the absence of chemicals. The two most frequent types of DNA lesions (cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6–4) pyrimidine photoproducts (6-4 PPs)) are known to be induced by UVB (290–320 nm) and UVC (190–290 nm), and unrepaired dimers were found to be mutagenic (7). The presence of chemicals sometimes induces changes in the conformation of DNA in the nucleus, which is dependent on DNA binding proteins, and the epigenetic changes may influence the formation and repair of pyrimidine dimers (Fig. 1C). The frequency of UV-induced lesions at specific sites was shown to be modulated by nucleosomes and other DNA binding proteins approximately twenty years ago (8). We recently demonstrated that modifications to histones, the main DNA binding proteins, altered sensitivity to UV and suppressed the repair of CPDs (9). Some environmental chemicals, hormones, and metals have been shown to affect histone modifications.

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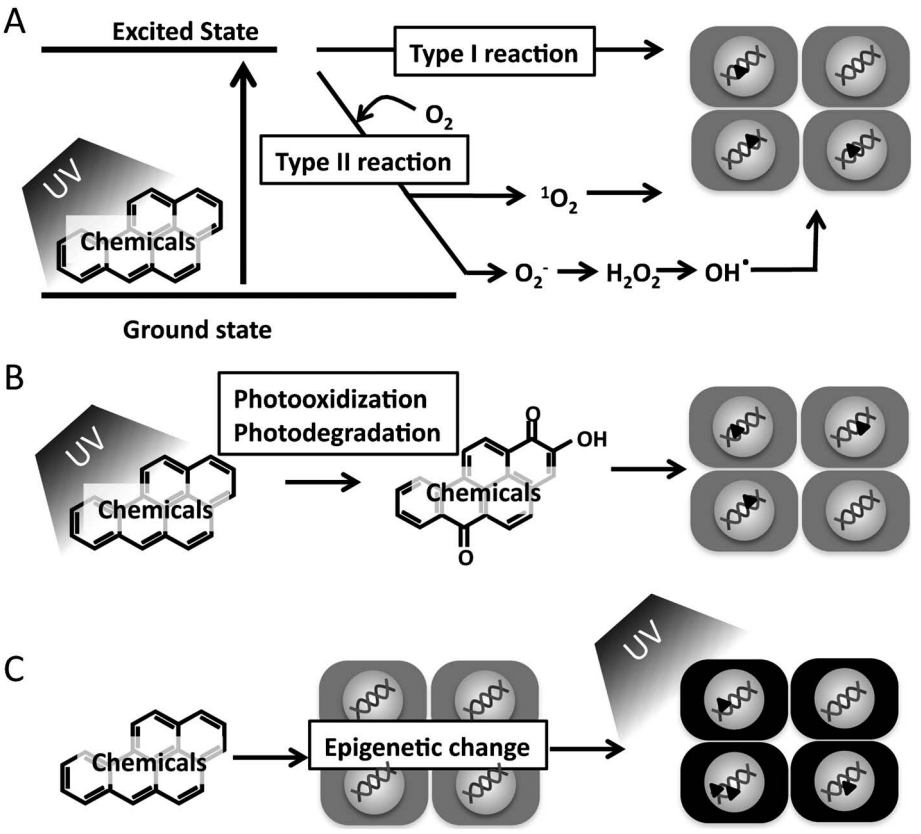

Fig. 1. Possible pathways for photogenotoxicity. We proposed three pathways for photogenotoxicity. (A) General photogenotoxicity; the ability of chemicals to induce genotoxic effects when irradiated with UV and/or visible light. (B) Genotoxicity induced by photooxidized or photodegraded chemicals. (C) UV-induced genotoxicity after pre-exposure to chemicals. Chemically-induced epigenetic alterations may influence the formation and repair of UV-induced pyrimidine dimers.

We herein focused on the third pattern (Fig. 1C) of photogenotoxicity. The relationships between the histone modifications induced by chemicals and UV-induced DNA damage and repair have been discussed as a new aspect of the photogenotoxicity of chemicals.

Histones and Structure of Chromatin

Genomic DNA in eukaryotic cells winds around histones to form nucleosomes, which are then packaged into the condensed structure of chromatin. The fundamental unit of chromatin, the nucleosome, consists of an octamer of the four core histones (two each of H2A, H2B, H3, and H4) around which approximately 146 base pairs of DNA are wrapped. Histones contain a large proportion of the positively charged amino acids, lysine and arginine in their structure. DNA is negatively charged due to the phosphate groups. These opposite charges result in the high binding affinity between histones and DNA, and condense the structure of chromatin.

The structure of chromatin allows a genome to fit into the small volume of the nucleus in its condensed form, but must also allow the proteins involved in transcription, replication and repair to access DNA. Therefore, the condensed structure of chromatin has to be temporarily relaxed (10). Histone modifications play a role in this relaxation. Over 100 distinct post-translational histone modifications, including lysine methylation, lysine acetylation, and serine/threonine phosphorylation, have been identified to date (11,12). These modifications, which mainly occur on the N-terminal tails that protrude from the nucleosome, can affect nucleosome interactions, and, when combined, may change the structure of chromatin, thereby regulating cell functions and responses.

The acetylation of histones is the most extensively examined histone modification. Acetylation occurs in lysine residues and neutralizes the positive charge. This weakens charge-dependent interactions between a histone and DNA. A previous study reported that acetylation of the lysine residue in the histone H4 tail *in vitro* markedly reduced its affinity for DNA (13). In eukaryotic cells, the relaxation of chromatin due to the acetylation of lysine in histones increased the accessibility of several proteins to DNA, leading to the transcription and replication of DNA (14,15). The relaxation of chro-

matin is also necessary to increase the access of repair proteins to damaged DNA, and has been discussed in a later section.

UV-induced DNA Damage and Repair

UV radiation is one of the most prevalent inducers of DNA damage in our environment. The UV spectrum has been divided based on wavelength: UVA (320–400 nm), UVB (280–320 nm), and UVC (200–280 nm). UVC and some UVB are absorbed in the stratospheric ozone layer, whereas UVA and most UVB reach the earth's surface. UVB produces two major pyrimidine (thymine and cytosine) photoproducts, CPDs and 6-4 PPs (7). UVA has also been shown to induce the formation of CPDs, which are frequently generated at thymine-thymine dipyrimidines (16,17).

Pyrimidine dimers are primarily repaired by nucleotide excision repair (NER). In eukaryotic cells, NER has been divided two pathways: global genomic repair (GGR) and transcription-coupled repair (TCR). GGR surveys the entire genome for distorted DNA lesions, whereas TCR is selective for the transcribed DNA strand in actively expressed genes (18). The fundamental difference between the two NER pathways is the manner in which lesions are recognized. Both the UV-DDB heterodimer (DDB1-DDB2/XPE) and XPC-HR23B complex are responsible for this in GGR, while an RNA polymerase stalled at the sites of DNA lesions and certain specific factors, such as CSA, CSB, and XAB2, is in TCR. Most subsequent steps in both processes use the same enzymes (18). Xeroderma Pigmentosum group B and D helicases (XPB and XPD) unwind the DNA duplex, and XPA is then recruited to stabilize the repair complex and orient the dual incision of the DNA lesion by two structure-specific endonucleases, XPG and ERCC1-XPF. A section of single stranded DNA with a gap of 25–30 nucleotides is removed and the gap is then filled by DNA synthesis and ligation via DNA polymerase.

Although the core mechanism of NER is relatively well known, as described above, the mechanism by which the repair proteins detect DNA lesions and access condensed chromatin remains unknown (19). Previous studies demonstrated that pyrimidine dimers were processed at faster rates in nucleosome-free regions and in linker DNA than in the internal protected regions of nucleosomes in yeast (20,21). Rearrangement of the nucleosome structure following the excision repair of UV-induced photoproducts in chromatin was reported in mammalian cells over two and a half decades ago (22). The findings of this study suggested that nucleosome rearrangements may regulate the rate of repair synthesis. In *in vitro* studies using plasmid DNA, NER was found to be less efficient in reconstituted nucleosomes than in naked DNA (23,24), which indicated that the tight nucleosome structure on damaged DNA inhibited the ability of molecules involved in NER. These findings suggested that NER needed changes to occur in nucleosome interactions at the damaged sites so that repair molecules could access the damaged DNA easily. Transcriptional activity has also been correlated with the efficiency of NER because a change in the structure of chromatin is needed for transcription. The degree of silencing of a specific gene has been shown to directly modulate the efficiency of NER (25). CPDs are repaired more rapidly in transcribed strands than in the inactive strands of some genomes (26,27). In hamster cells, 80% of the dimers were removed from the transcribed strand within 4 h, whereas few were removed from the non-transcribed strand even after 24 h (27). The histone modifications associated with transcription may influence TCR (28,29). Deletion of the histone acetyltransferase (HAT), GCN5 affected the repair of CPDs in specific genes in which GCN5 plays an important role in transcription, whereas no detectable defect was observed in the overall repair of the genome. Teng *et al.* (28) speculated that histone acetylation allowed efficient access of the repair machinery to chromosomal DNA damage either indirectly by influencing transcription or directly by modifying the structure of chromatin irrespective of transcription. Histone modifications, particularly acetylation, may influence the activity of NER by altering nucleosome interactions, and this has been related to the accession of DNA repair molecules to DNA lesions.

UV-induced Histone Acetylation and NER

The relationship between histone modifications and the repair of DNA damage, including DSBs and pyrimidine dimers, has been examined in detail (30,31). It is a consensus of opinion that the acetylation of histones occurs following UV irradiation, and this is an important process for NER.

In the 1980s, Ramanathan and Smerdon (32) showed that nuclear proteins were hyperacetylated in UV-damaged cells and revealed the relationship between nuclear protein acetylation and NER. UV irradiation markedly acetylated histone H3 at lysine 9 and lysine 14 within 20 min (33). The normal pattern of histone H3 acetylation at lysine 9 consisted of bright dots on a very low staining background, while UV irradiation changed it to more diffuse nucleoplasmic staining (34). These findings indicated that the acetylation of histone that was only observed in actively transcribed DNA regions, spread throughout the nucleus following exposure to UV with global chromatin relaxation. Previous studies demonstrated the binding of HAT to DNA damage sites (35). UV-irradiation recruited GCN5 to DNA damage sites and induced the acetylation of histone H3 at lysine 9 (36,37). The knockdown of GCN5 resulted in the im-

paired recruitment of NER factors to the sites of DNA lesions and inefficient DNA repair. The transcriptional coactivator, TATA-box-binding protein-free TAF-containing complex (TFTC) containing GCN5 preferentially bound UV-irradiated DNA and acetylated histone H3 (38). Histone H3 at lysine 9 and/or 14 in yeast was also hyperacetylated by GCN5 in response to UV-induced DNA damage (39,40). The GGR complex was previously shown to regulate UV-induced histone H3 acetylation by controlling the accessibility of GCN5 in chromatin (41). These findings indicated that histone acetylation induced by UV exposure may promote the chromatin remodeling necessary for efficient NER, which may, in turn, provide an insight into how GGR and TCR are operated in chromatin.

Hyperacetylation by Histone Deacetylases (HDAC) Inhibitors (HDACi) and NER

HDAC are enzymes that regulate the acetylation status of core nucleosomal histones by catalyzing the removal of acetyl groups mainly from their amino-terminal residue (42,43). The inhibition of HDAC results in the accumulation of histones acetylated by HAT. Sodium butyrate (SB), trichostatin A (TSA), suberoylanilidehydroxamic acid, and valproic acid are prevalent HDACi, and treatments with those inhibitors can produce artificially hyperacetylated histones. HDACi have been attracting attention as a promising new class of antineoplastic agents for the treatment of solid and hematological malignancies. The use of HDACi in combination with cytotoxic agents including ionizing radiation and anticancer drugs has been a focus of attention for the effective induction of cell death (44,45).

A previous study suggested that SB may be able to hyperacetylate histones (9); however, the frequency by which pyrimidine dimers are formed in relation to normal histones as well as the repair ability remain unknown (Fig. 2). Hyperacetylation may change the structure of chromatin to its relaxed form; therefore, the repair of DNA damage may be easily predicted by the accessibility of repair molecules to damaged sites. However, a pretreatment with SB strongly induced cell death (apoptosis) within 24 h of UV irradiation (9). The number of CPDs formed following exposure to UV was the same in the presence or absence of SB, whereas the repair kinetics of CPDs was markedly slower in SB-pretreated cells than in untreated cells. Our result was inconsistent with the theory that histone acetylation relaxes the chromatin structure and changes the accessibility of DNA repair molecules to DNA damaged sites. In the 1980s, the unscheduled synthesis of DNA was shown to be enhanced in human fibroblasts pretreated with SB (46). Smerdon *et al.* (47) indicated that SB stimulated the initial rate of NER in both normal and repair-deficient human cells at concentrations at which histones were maximally hyperacetylated. Repair synthesis was approximately 1.8-fold higher in nucleosomes with an average 2.3 acetyl residues /H4 molecules than in those with 1.5 or 1.0 acetyl residues/ H4 molecules (48). On the other hand, there are the controversial reports that are similar with our results. SB enhanced cell death following UV irradiation in XP-A, XP-C, and normal cells, but suppressed it in XP-F cells (49). Another HDACi, trichostatin A (TSA) also enhanced sensitivity to UV-induced apoptosis (50). The use of HDACi is effective in combination with ionizing radiation and anticancer drugs (51–53). HDACi radiosensitized human melanoma cells by suppressing DNA repair activity (51,52). Loosening the chromatin structure via histone hyperacetylation was suggested to increase the efficiency of several anticancer drugs targeting DNA (53). We previously demonstrated that HDACi did not change the frequency by which CPDs formed, while the suppression of DNA damage repair was limited to damaged DNA using NER for repair (9). We proposed the following mechanism; histones may be partially acetylated around the sites of pyrimidine dimers after UV irradiation in order to improve access for repair

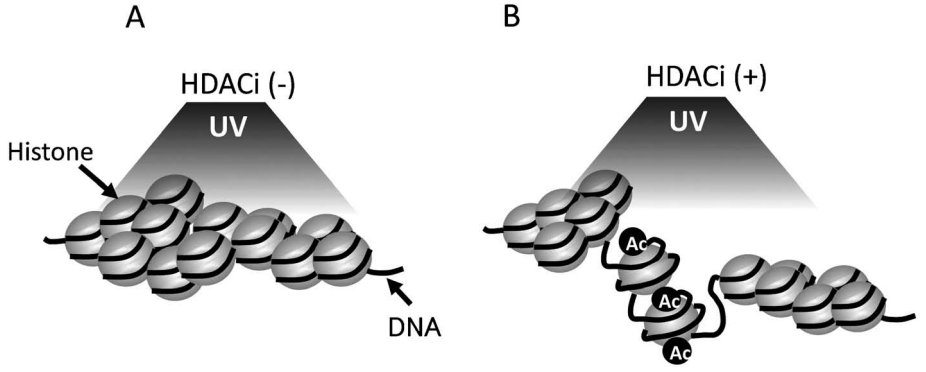

Fig. 2. Formation and repair of UV-induced pyrimidine dimers when histones are hyperacetylated by HDACi. A treatment with the HDACi, SB generated the global acetylation of histones. UV irradiation formed the same amount of CPDs regardless of hyperacetylation. On the other hand, the repair of CPDs was delayed in hyperacetylated cells (9). A: in the absence of HDACi, B: in the presence of HDACi.

molecules, as described in the previous section. Under the hyperacetylation condition induced by HDACi, the acetylation induced by formation of pyrimidine dimers after UV irradiation could not be induced because the histones may have already globally acetylated. Therefore, the repair molecules may not be able to find damage sites, resulting in the suppression of NER. This is mere speculation; however, the dysregulation of histone modifications would affect the formation or repair of pyrimidine dimers.

Histone Modifications by Chemicals

Previous *in vitro*, animal, and human studies demonstrated that several environmental chemicals changed epigenetic markers such as DNA methylation and histone modifications. (54,55). Most studies conducted to date have focused on DNA methylation, whereas few have examined environmental chemicals in relation to histone modifications. In histone modifications by chemicals, many studies have investigated metal-induced histone modifications. Sodium arsenite was previously shown to increase global histone acetylation, and this was associated with the inhibition of HDAC activity (56). They demonstrated that relaxing of the chromatin structure by arsenite may play a significant role to impart its genotoxic effects. Acetylation also induced the proto-oncogenes, *c-fos* and *c-jun* (57). In contrast, Ge *et al.* (58) reported that the arsenic metabolite, monomethylarsonous acid decreased global histone acetylation by activating HDACs and found that the dysregulation of histone acetylation may be a key mechanism in monomethylarsonous acid-induced malignant transformations and carcinogenesis. Chromium and nickel also reduced histone acetylation (59,60). Ke *et al.* (59) described other nickel-induced histone modifications such as ubiquitination and methylation, and suggested that these may be associated with nickel-mediated carcinogenesis. The endocrine-disrupting chemicals, tributyltin and triphenyltin, but not monobutyltin, monophenyltin, or inorganic tin enhanced HAT activity (61). Previous studies demonstrated pesticide-induced histone acetylation (55,62,63). Dieldrin induced the acetylation of histones H3 and H4 within 10 min of its exposure, and this was attributed to a dieldrin-induced proteasomal dysfunction that resulted in the accumulation of HAT (62). Paraquat also acetylated histone H3, but not H4, and this was attributed to a decrease in HDAC activity (63); this acetylation may have regulated cell death because a HAT inhibitor protected against apoptotic cell death induced by paraquat.

Hormones were also shown to induce histone acetylation in the 1970s (64,65). 17-β-estradiol (E2) acetylated histones in the rat uterus immediately after its administration (64). Phytoestrogens such as genistein and daidzein were also found to acetylate histones, similar to E2 (66). Aldosterone rapidly increased histone acetylation, whereas progesterone did not (65). We recently reported that E2 induced global histone acetylation in MCF-7 and HaCaT cells in time- and dose-dependent manners (data not shown). As described above, HDACi induced global acetylation, and the repair of CPDs following UV irradiation was delayed (9). UV was applied to the hyperacetylated histones after the E2-treatment. The E2-treatment increased sensitivity to UV, which suggested that hyperacetylation may contribute to suppressing the repair of pyrimidine dimers. This is now being examined in more detail.

Histone modifications by chemicals may affect the ability of DNA damage to be repaired. Interactions between UV-induced genetic and chemically-induced epigenetic changes may enhance or prevent mutagenicity and carcinogenicity. Therefore, these are important points in 'photogenotoxicity'.

Conflicts of interest statement: The author declares that there are no conflicts of interest.

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