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UV DAMAGE, DNA REPAIR AND SKIN CARCINOGENESIS

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1. ABSTRACT

Skin cancer is unique among human cancers in its etiology, accessibility and the volume of detailed knowledge now assembled concerning its molecular mechanisms of origin. The major carcinogenic agent for most skin cancers is well established as solar ultraviolet light. This is absorbed in DNA with the formation of UV-specific dipyrimidine photoproducts. These can be repaired by nucleotide excision repair or replicated by low fidelity class Y polymerases. Insufficent repair followed by errors in replication produce characteristic mutations in dipyrimidine sequences that may represent initiation events in carcinogenesis. Chronic exposure to UVB results in disruption of the epithelial structure and expansion of pre-malignant clones which undergo further genomic changes leading to full malignancy. Genetic diseases in DNA repair, xeroderma pigmentosum, Cockayne syndrome and trichothiodystrophy, show varied elevated symptoms of sun sensitivity involving skin cancers and other symptoms including neurological degeneration and developmental delays. In humans, only xeroderma pigmentosum shows high levels of cancer, but mouse strains, with any of the genes corresponding to these diseases knocked-out, show elevated skin carcinogenesis. The three major skin cancers exhibit characteristic molecular changes defined by certain genes and associated pathways. Squamous cell carcinoma involves mutations in the p53 gene; basal cell carcinoma involves mutations in the *PATCHED* gene, and melanoma in the p16 gene. The subsequent development of malignant tumors involves many additional genomic changes that have yet to be fully cataloged.

Table 1. Incidence of non-melanoma skin cancer in Caucasian populations per 100,000

Location	SCC	BCC	Reference
Minnesota 1984/86	136 (m)[1]; 46 (f)[1]	-	189
Minnesota 1990/92	106 (m); 100 (f)	-	189
Minnesota	-	175 (m); 124 (f)	190
Detroit (42°N)	30	-	191
New Orleans (30°N)	154		191
Portland, OR	81.2		192
Australia	160	652	8
	-	849 (m); 605 (f)	9

1. m, male; f, female.

2. INTRODUCTION TO SUNSHINE AND SKIN CANCER

The major factor in human skin cancer incidence is, undoubtedly, exposure to the sun (1, 2). Historical evidence indicates that the role of sun exposure was recognized over a century ago (for detailed references see (3)). Thiersch, in 1875 suggested the link between sunlight exposure and the subsequent development of skin cancer. Unna in 1894 stimulated widespread interest in the importance of sunlight as a cause of chronic skin changes including the development of skin tumors. Hyde in 1906 reported the results of his study on the prevalence of skin cancer in people of different occupations and geographic locations. He deduced that sunlight alone was responsible for the appearance of carcinoma in some people. Dubreuilh recognized that skin pigmentation played a significant role in the development of skin cancer, since lightly pigmented people developed more cancers than those with darker pigmentation.

There are three main forms of cancer involving the cells of the skin: squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and melanoma. New SCCs occur in the US population at about 200,000 per year; BCCs at about 10^6 per year and are the commonest human cancer (table 1). New melanomas occur at about 50,000 per year and generally arise from melanocytic nevi, and there is a correlation between the number of nevi arising from childhood sun exposure and melanoma risk. Melanoma, although also associated with sunlight exposure, shows a weaker dependence on total exposure to sunlight and a distribution over the body that is not correlated to exposed areas (4, 5).

That said, there are many variations in susceptibility to skin cancer that depend on the particular cancer type, age at exposure, ethnic group and skin color, latitude, lifestyle and work environment, clinical treatments and genetics of the individual. Several other causative factors have also been shown to play a role including arsenic, heat, x-rays, scars and viruses. Skin cancer is also one of the unexpected consequences of our increased world-wide mobility as a species, especially for fair-skinned individuals. Significant risk factors for skin cancer in the general population include: latitude of residence, age of migration, ethnic origin, skin color, a tendency to burn or tan. SCCs and BCCs are found on sun-exposed parts of the body (e.g., the face and trunk in men, face and legs in women) and their incidence is correlated with cumulative sunlight exposure. SCCs are often preceded by actinic keratoses that are indicators of cumulative solar exposure. Tumor incidence and mortality increase with decreasing latitude, corresponding to exposure; skin cancers are less frequent in dark-skinned populations than in lighter-skinned peoples; and tumor incidence increases with occupational exposure, such as in ranchers and fishermen.

In previous centuries, especially over the 5 million years of hominid evolution, migration was relatively slow and skin color could equilibrate to the solar intensity of the particular lattitude and climate. Equilibrium could be established between harmful effects of solar exposure that affected reproduction (e.g. birth defects from photo-destruction of folic acid) and beneficial effects (e.g. vitamin D synthesis) that resulted in lesser pigmentation as populations lived further away from the equator (6). Equilibrium between skin color and solar exposure is estimated to take approximately 10,000 years and involves changes in the activity of a small number of genes along the melanin biosynthetic pathway. Human skin is consequently classified into multiple types (e.g. I to IV) ranging from individuals who always burn and never tan, to those who tan but never burn; skin cancer susceptibility varies accordingly (7). The indirect effect of the equilibration of skin type and solar exposure was also pigmentary protection against the carcinogenic effect of sun exposure. Since skin cancers generally occur later in life they may have a lesser effect in evolutionary terms on human reproductive rates. The epidemic of skin cancers in the 20th century can therefore be linked to the increased mobility of Caucasian populations during the centuries of European exploration and settlement in areas of the world for which their skin is poorly adapted (6).

Geographically, there is a direct association between the amount of solar radiation and the incidence of skin cancer in light-skinned individuals in a population (table 1). This association is seen most notably in Australia where massive public service campaigns were instituted because skin cancer rates were increasing to epidemic proportions (8, 9). Additionally, African albinos develop skin cancers much earlier and in greater numbers compared to their counterparts with normal skin pigmentation (10). Epidemiologic evidence also shows that people who spend most of their time outdoors have higher incidences of skin cancers than those who do not. This fact was emphasized in a 1990 study of Maryland watermen, a relatively homogenous group of Caucasians who make their living by fishing in the Chesapeake Bay (11). The subsequent development of SCC correlated directly with an individual's UV exposure. Pale skin and red hair are risk factors for the development of both BCCs and SCCs, but UV exposure in the 10 years prior to development of skin cancer was only a risk factor in the development of squamous cell carcinoma (12).

A recent hypothesis for the role of exposure conditions on skin cancer production suggests two important hypotheses (1). One, the pattern of exposure, intermittent or steady, and the total accumulated exposure are independent variables in determining cancer incidence. Second, exposure before the age of 10 affects the lifetime potential for skin cancers, although exposures later in life affect the extent to which this potential is realized. These are based on the observation that the risk for various skin cancers as a function of total accumulated dose of solar UV is in the order SCC > BCC > melanoma. The risk as a function of the frequency of intermittent sun exposure, given the same total dose is, however, reversed: melanoma > BCC > SCC. These relationships can have paradoxical outcomes in that reducing occupational exposure but increasing intermittent recreational exposure could reduce SCC but increase melanoma. The experience in Australia, from the cancer risk as a function of the age of immigration, is the strongest evidence for a role of childhood exposure in skin cancer (1, 5). Overlaid on this effect of childhood exposure is the observation that UV exposure later in life may have additional promoting effects on skin carcinogenesis through short-term responses to the exposures (13). These may include a major immunosuppressive effect of UV exposure leading to loss of antigen-presenting Langerhans cells and the appearance of dyskeratotic keratinocytes (apoptotic sunburn cells) in the upper epidermis, together with the erythemal sunburn response associated with vasodilation caused by a release of prostaglandin (14). Another example of the potential role of the immune system in skin cancer is the large increase in SCC found among organ transplant patients, that can reach 40-70% 20 years after transplantation (15).

The most dramatic examples of variations in human susceptibility to skin cancer occur in human genetic disorders that show increased responses to sunlight exposure (16). These include xeroderma pigmentosum (XP), Cockayne syndrome (CS), trichothiodystrophy (TTD), basal cell nevus syndrome (BCNS), dysplastic nevus syndrome, Rothmund-Thompson syndrome,albinism, the porphyrias, and phenylketonuria. Some other disorders are associated with an acquired sun sensitivity, including polymorphous light eruption, actinic reticuloid, solar urticaria, lupus erythematosus, and Darier's disease.

3. UV PHOTOCHEMISTRY

Action spectra for squamous carcinoma indicate that DNA is the target molecule; the absorption spectrum of DNA correlates well with lethality, mutation induction, and photoproduct formation (17-22). The wavelengths of solar UV most important for carcinogenesis, however, fall in the range 300-380 nm. Atmospheric ozone blocks solar UV light at around 300nm, setting the lower limit. Absorption in proteins and nucleic acids peak at 280 and 260 nm respectively, so that their absorption is falling rapidly with increasing wavelength, above 300nm. The overlap between the shorter wavelength end of the solar emission spectrum and the longer wavelength arm of the absorption curves of macromolecules is the region where most biologically significant absorption occurs. Within this overlap UV is split into UVA and UVB ranges. UVA is the longer wavelength range (320-400 nm) where most absorption is through highly reactive chemical intermediates, oxygen and hydroxyl radicals, which indirectly cause damage to macromolecules. The shorter wavelength range, UVB (280-320 nm), is directly absorbed in DNA and protein. The most important factor for carcinogenesis is the DNA absorption, that produces specific pyrimidine photoproducts.

The energy absorbed by DNA produces molecular changes that involve single bases, interactions between adjacent and nonadjacent bases, and between DNA and proteins (22). The relative proportions of DNA photoproducts can be very sensitive to wavelength. The major photoproducts produced by UVB are dimerizations between adjacent pyrimidines. Cyclobutane pyrimidine dimers (CPDs) are the more common, with [6-4] pyrimidine-pyrimidinone photoproducts [(6-4)PPs] representing about 25% the frequency (22). The distribution of both photoproducts in DNA depends on base sequence, secondary structure, and DNA-protein interactions. Cytosine absorbs more efficiently at longer wavelengths than thymine, such that C-containing photoproducts are more common after UVB irradiation (23). Cytosine CPDs and [6-4]PPs, which are preferentially induced at thymine-cytosine dipyrimidines, therefore play a major role in UVB mutagenesis, (24). Methylation at PyrCG sequences in the p53 gene increases the formation of CPDs at sites that are hotspots for mutations (25). The [6-4]PP undergoes additional photochemical reactions after UVB resulting in production of a photoisomer, the Dewar pyrimidinone (26). Many chemicals and pharmaceuticals are known to induce inflammatory responses and some act as photosensitizers in the production of DNA photoproducts in the skin, e.g. benzophenone, ketoprufen and fenofibrate (27).

Other minor photoproducts include purine-purine and purine-pyrimidine photoadducts, photohydrations, and photooxidations (28). The total yield of these photoproducts is only 3-4% of the yield of CPDs, and their biological role is likely to be unimportant in most cases (22). They may, however, behave as premutagenic lesions in specific sites. The [6-4]PPs produce much greater distortions in DNA than CPDs, and are more immunogenic when irradiated DNA is used to raise antibodies. Some conditions, especially dehydration and binding of unique proteins, can change DNA conformation and result in other kinds of UV photoproducts being formed. In bacterial spores, for example, DNA adopts a special conformation similar to dehydrated DNA and is surrounded by small acid-soluble spore proteins, such that a unique photoproduct is formed, 5-thyminyl-5, 6-dihydrothymine (29).

The importance of base damage, strand breaks and DNA-protein crosslinks formed by UVA is not known, but these may be important consequences of sunlight exposure. These may be more important in photoaging, for example, than DNA photoproducts formed by UVB. Cell killing and mutation induction have been observed in

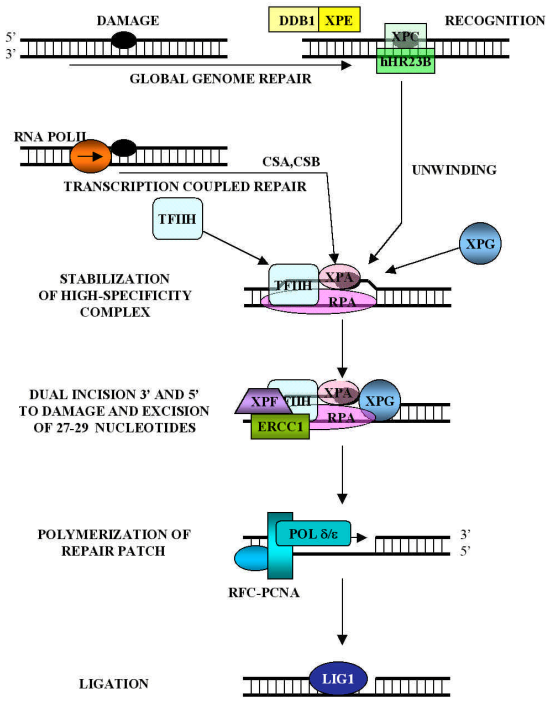

Figure 1. Model for the sequential assembly of the various components of nucleotide excision repair. Global genome repair involves the initial binding of the XPC-hHR23B and XPE binding proteins followed by downloading of the TFIIH transcription and helicase complex that remodels the damaged site. Transcription coupled repair involves initial response to damage by stalling of the RNA polymerase II apparatus, and coupling by the CSA and CSB proteins. Subsequent steps proceed in common, consisting of loading the XPG nuclease, the XPA-RPA DNA binding proteins, and the ERCC1-XPF nuclease. After nuclease cleavage around the dimer site, the excision complex departs and the site is resynthesized by PCNA-polymerase delta and ligase I. Figure has been redrawn (37) with addition of the transcription repair pathway.

human epidermal cells after irradiation with UVA light (17, 19) which may not be mediated by DNA damage (30, 31) because free radical scavengers can protect against cytotoxicity (32). UVA light can cause significant levels of tumorigenesis in hairless mice and the dose responses seem to indicate a different mechanism from pyrimidine dimer and [6-4]PP formation (33).

4. THE MECHANISM OF NUCLEOTIDE EXCISION REPAIR

The increased frequency and reduced latent time of all forms of skin cancer in sun-exposed patients suffering from the inherited DNA repair disorder XP was the most direct evidence for the role of UVB in human skin cancer (4, 34). Most XP cells lack the main repair system for UV damage: nucleotide excision repair (NER). Identification of the genes and biochemical pathways involved in the UV responses in XP cells have helped to elucidate the basic mechanisms of NER (16, 35, 36).

Pyrimidine CPDs and [6-4]PPs produced in DNA by UVC or UVB radiation are repaired by a complex multistep process involving many interacting gene products. In part, it is the need for interacting proteins in repair that gives rise to complex overlapping symptoms in some patients with mutations in these genes. These processes involve sequential steps of photoproduct recognition, assembly of the DNA binding proteins, remodeling by helicases and excision nucleases, displacement of the excised fragment, and polymerization of the replacement patch (37) (Figure 1). The efficiency of NER is determined by the particular photoproduct, the bases flanking the damage, DNA conformation, bound proteins, transcriptional activity of both the gene and DNA strand containing the damage, and additional factors including p53, GADD45, and others (38, 39). The [6-4]PPs are rapidly excised, 50% being removed in only a few hours. CPDs, however, are much more slowly removed and it takes 12 to 24 h to reach a 50% removal overall (40, 41). The rate of excision of photoproducts, therefore, represents a dynamic balance between strand breakage and rejoining, subject to many modulating factors on an individual nucleotide and gene basis. Only a small fraction of dimers are acted upon at any one time and the process removes them sequentially over a long period. In part the excision of CPDs may be delayed because the strong affinity of the excision system for [6-4]PPs initially sequesters available enzymes.

The NER pathway removes pyrimidine CPDs and large chemical adducts in DNA by a complex recognition and nucleolytic process and replaces the site with a newly synthesized region (37, 38, 42, 43). The repair process, in principle, involves removal of a 27-29 nt oligonucleotide containing the photoproduct by precisely positioned cleavages 5 nt on the 3' side of the photoproduct, and 24 nt on the 5' side (44). Once this oligonucleotide is removed, the resulting gap is filled in by DNA polymerase delta, proliferating cell nuclear antigen (PCNA) and single strand binding protein and ligase (38). The individual factors of NER associate sequentially and independently on UV photoproducts, to a first approximation, without preassembly of a “repairosome” complex (37, 45). The basic components of the process include the XPA protein, the heterotrimeric replication protein (RPA), the 6 to 9 subunit TFIIH, the XPC-hHR23B complex, the XPG nuclease, and the ERCC1-XPF nuclease (38). After assembly the XPC-hHR23B complex dissociates and the XPG protein cuts 3' to the lesion and the ERCC1-XPF heterodimer cuts 5' to the CPD. The nuclease complex plus the 29-30 nt single strand fragment is released by the action of transcription factor TFIIH which contains both 3'-5' (XPB) and 5'-3' (XPD) helicases.

Two major branches of NER are distinguished by the relationship to transcriptional activity of the genes being repaired described as transcription-coupled repair (TCR) and global genome repair (GGR) (figure 1). The initial damage recognition mechanism for TCR may be the stalled RNA pol II, itself. Two genes, *CSA* & *CSB*, are involved specifically in TCR. CSA contains WD-repeat motifs that are important for protein-protein interactions

(46). CSB contains an ATPase activity, helicase motifs, and a nucleotide binding domain, but only the latter is essential for TCR (47). UV damage in CS cells results in a failure of DNA and RNA synthesis to recover to normal levels after UV irradiation (48). The excision of DNA photoproducts from total genomic DNA of CS cells is normal, but repair of transcriptionally active genes is reduced (49). CPDs are excised more rapidly from actively transcribed genes, especially from the DNA strand used as the template for transcription (50). This strand preference also requires the action of components of the mis-match repair (MMR) system whose major role is correcting mis-matched bases generated through replication errors or deamination of cytosine, and can discriminate parental from newly synthesized DNA strands (50, 51). In addition, a basal transcription factor, TFIIH, plays a major role in repair and many of its components are directly involved in remodeling the damaged regions for excision to occur (52). Using ligation-mediated PCR to carry out a base by base analysis of excision in the promoter and early region of the PGKI gene revealed that excision is slow where binding proteins interact with the promoter and increases immediately after the ATG start site for transcription (53).

The initial damage recognition factors uniquely required for GGR are the XPC and XPE DNA binding proteins. The XPC-hHR23B complex (54, 55) is the earliest damage detector to initiate NER in nontranscribed DNA, acting before the XPA protein, and serves to stabilize XPA binding to the damaged site with a high affinity for the [6-4]PP (56, 57). The XPC protein may be required for transient nucleosome unfolding during NER (58). This complex is specifically involved in GGR but not TCR. Stable association of TFIIH with DNA lesions is dependent on the integrity of XPA and XPC proteins. The XPE protein has similar binding characteristics to photoproducts as XPA and XPC but plays a much less prominent role. XPE is a heterodimer of a p48 which is found to carry mutations from several XPE patients, and a p125 protein (59). The p48 subunit is inducible in human cells in a p53-dependent manner and is not expressed in hamster cells that fail to repair CPDs in nontranscribed DNA (60).

The XPG protein is also required for TCR of oxidative damage (61). At least one component of TFIIH, XPB, interacts with p53 and initiates a signal cascade leading to apoptosis in damaged cells (62). The whole NER process requires about 100 nt of DNA along which to operate *in vitro* (44). PCNA, which is required for repair synthesis, also interacts with GADD45, a damage inducible protein, which stimulates excision repair *in vitro*, though its *in vivo* function is not known (63). Although many of the components of NER are involved in a variety of sun-sensitive and developmental disorders, several components, especially the genes *ERCC1* (64, 65) and *hHR23B* (55) have not been found in a clinical setting. Knockout of the genes in mice has shown that several of the genes are essential for embryo development (66).

5. MUTAGENIC POLYMERASES AND DNA REPLICATION

DNA photoproducts are blocks to the replicative DNA polymerases, alpha, delta and epsilon which cannot accommodate large distortions such as DNA photoproducts or adducts in their active sites (67, 68). Replicative bypass of these photoproducts is achieved instead by damage-specific polymerases with relaxed substrate specificity, now defined as class Y polymerases (35, 69). Three members of class Y have been identified in the mammalian genome, *POL H, I,* and *K*. *POL H* and *I* are close homologs, unique to mammalian cells, and only a single *POL H* gene is found in yeast (69). Pol I has a poorer capacity for replication of UV damage and Pol K seems completely unable to replicate UV damage. These polymerases have larger active sites that allow them to read-through noninformative sequence information resulting from DNA damage (70). The consequence is that these polymerases have high error rates of the order of 1% when assayed *in vitro*, and this property must be controlled *in vivo* otherwise the results would be catastrophic to the cell (71, 72). Control is achieved by several mechanisms for Pol H. First, the enzyme is excluded from the replication fork until replication is stalled by UV damage, at which point Pol H traffics into the nucleus and accumulates in foci at the replication fork (73, 74). This requires specific sequence motifs in the protein for translocation and for binding to PCNA (73, 75). Pol H acts distributively, and is only able to extend the nascent DNA chain by one or two bases across from the photoproducts, and there may be a role for editing by a separate exonuclease. This results in the addition of adenines across from thymine-containing photoproducts resulting in accurate replication of a T-T pyrimidine dimer.

The terminus of a growing DNA strand that has replicated a T-T dimer by the action of Pol H has poor base-pairing between the adenines in the new strand and the thymines of the dimer. This partial mis-match can be extended by a high fidelity DNA polymerase, Pol Z, which is able to extend from a mismatch (76, 77). Pol Z is a heterodimer consisting of the catalytic component hRev3 and hRev7. Replication of UV damage also involves a deoxycytidyl transferase hREV1p found in close association with Pol Z (78). The hRev 7 component may serve to regulate the activities of hRev1 and hRev3, and is also found to interact with the spindle assembly checkpoint protein hMAD2 (78, 79). Loss of Pol H results in an increase in the error rates in replication of damaged DNA, due to the requirement for cells to use additional backup processes (76, 80). In contrast, loss of hRev1 or Pol Z results in a decrease in mutation rates (81, 82).

Mutations in *POLH* are found in the XP variant complementation group of XP (81, 82). Consequently XPV cells are arrested in DNA replication at pyrimidine dimer sites, and this phenotype was well known for many years before the existence of the class Y polymerases was identified (83, 84). UV irradiation of XPV cells results in elevated mutation rates in chromosomal and plasmid-borne genes, with increased insertion of adenines (85). DNA replication in XPV cells is modulated to a large extent by p53 functions (86). In transformed XPV cells with compromised p53, arrested replication forks collapse into double strand breaks and recruit components of the nonhomologous endjoining pathway (87). This will

contribute to chromosomal instability in surviving cells that can contribute to malignant transformation.

Polymerase H preferentially inserts adenine in the nascent strand opposite the lesion (called the "A rule") and hence can accurately replicate a thymine-containing CPD (88, 89). This mechanism has two important implications regarding the mutagenicity of different photoproducts. First, mutations will most often occur where cytosine is a component of the photoproduct, since insertion of adenine opposite thymine is a correct and nonmutagenic event. Hence, most CPDs, because they form between two thymine bases, are nonmutagenic in the cell. Second, the more distortive a lesion is the more likely it will block DNA synthesis and result in a lethal rather than mutagenic event. Since the [6-4]PP is considerably more distortive than the CPD (i.e., it causes a 47^{o} as opposed to a 7^{o} helical bend) it is more likely to be lethal rather than mutagenic. Because damage bypass and adenine insertion depend on a variety of conditions, both CPDs and [6-4]PDs contribute to mutagenesis in a complex manner.

6. UV-INDUCED MUTAGENESIS

Mutations are the end result of an active process in which damaged sites in DNA are processed to minimize their toxic effects at the expense of their precise sequence. The frequency with which a dose of UV generates mutations depends on numerous factors including the particular photoproduct, flanking sequences, the efficiency of NER at that site, the cell's capacity to replicate the photoproduct, plus secondary effects depending on cell cycle checkpoints and other cellular and tissue level regulation. Despite these many factors that contribute to the yield and nature of mutations at any particular site, the photochemistry of DNA leaves an indelible mark on the mutation spectrum. In general, UV-induced mutations occur at dipyrimidine sites, particularly the 3'C of a TC or CC site, and tandem mutations occurring at both Cs of a CC site are distinctive signs that UV was the causative agent of a mutation (90).

The yield of mutations is increased in cells that lack NER or Pol H (91, 92), and in cells that lack mismatch repair (specifically MSH6, PMS2 or MSH2) (93). In cells that lack XPA for example the yield of mutations is increased and the spectrum shifted to different hotspots and a lower ratio of transitions to deletions (94). Mutagenesis is reduced in the absence of a functional polymerase Pol Z or deoxycytidyl transferase hRev1p (76, 80). Mutagenesis appears to be dependent on constitutive enzyme systems and is not induced by SOS-like systems seen in *E. coli*. For example, cotransfection of monkey cells with a mixture of an unirradiated *supF* plasmid and an irradiated plasmid without the *supF* gene did not generate mutations in the unirradiated vector (95).

A comparison of photoproduct yields, rates of repair, and mutations in the *PGKI*, *ras* and p53 genes, using ligation mediated polymerase chain reaction (LMPCR), has shown that regions of high UV-induced mutation can be caused by either or both high photoproduct yield and low repair (53, 96-99). The rate of excision repair of dimers at specific nucleotides in the promoter and exon 1 of the *PGK1* gene varied 15-fold with much reduced repair at transcription factor binding sites(53). DNA repair at individual nucleotides in the p53 tumor suppressor gene was highly variable and sequence dependent, with slow repair observed at seven of eight of the positions associated with mutations (96). UV-induced mutations in the p53 gene are important in development of squamous cell carcinomas and may arise at DNA repair "coldspots" rather than photoproduct "hotspots" (68, 100). A determining factor in mutagenesis, therefore, appears to be the persistence of damage, by a combination of rates of formation and of repair, through a subsequent period of DNA replication.

In the *supF* gene inserted into the mouse L cell chromosome (101) and in the endogenous *APRT* gene of CHO cells (102) most of the mutations consisted of C-to-T transitions occurring at T-C and C-C sequences. Due to the strand-specificity of repair, there is a bias between mutations in the coding and the non-coding strands of expressed genes that differs according to the NER capacity of the cells (103, 104). In mice with normal NER bearing a transfected *gpt* gene, UVB induced a higher mutation rate in the epidermis than the dermis (105). The majority of the mutations were transitions at dipyrimidine sites including tandem mutations, with a strong bias toward mutations in the template strand of the *gpt* gene (105). In XPA mice the bias toward mutations in the transcribed strand was greater than for wild type controls, and characteristic CC to TT tandem mutations could be detected in a transgene, *rpsL* (106).

Shuttle vectors allow separation of the damaged substrate from effects that might be caused by UV damage to the host cells. UV-irradiated plasmids are transfected into human and other cell types, where they are replicated by the host cells, and mutations occur. The mutations are therefore generated by the biochemical processes of repair and replication of the host cell, acting on a defined substrate set of lesions. Sites of mutations can then be compared with sites of photoproduct induction in the target sequence. These studies produce results that are similar to those obtained in *E. coli*: sites of transition mutations correlate with sites of increased [6-4]PP. Mutation hotspots in the *lacI* gene transfected into human cells were identical to those determined in *E. coli* (107) and a similar correlation occurred in the *supF* gene transfected into SV40-transformed human fibroblasts and monkey kidney cells (108). However, the overall yield of mutations is also dependent on pyrimidine dimers.

The identity of mutagenic lesions has been determined by enzymatic photoreactivation of the *supF* sequence in plasmids before transfection, which reverses pyrimidine dimers but not [6-4]PPs (95, 109). Photoreactivation reduced the mutation frequency in normal cells by 75% and in XP group A cells by 90%. A similar analysis with photoreactivation suggested that CPDs occurring at dipyrimidine sites containing at least one cytosine base were the predominant mutagenic lesions induced in human cells and that [6-4]PPs at these sites

accounted for only about 10% of the mutations (109). However, this same study indicated that the frequencies of both CPDs and [6-4]PPs at individual dipyrimidine sites did not correlate with mutation frequency, suggesting that, although UV-induced lesions are required for mutagenesis, mutation hotspots are determined by other factors.

UVB can also cause deletions, though these are much less prominent than from ionizing radiation where the major damage involves direct DNA breakage. In one study UVB irradiation of the epidermis of mice with normal NER produced large deletions that were about 75-fold less frequent than point mutations (110). The junctions of the deletions contained short regions of homology that are characteristic of those produced by nonhomologous endjoining reactions (NHEJ). These may be produced during replication arrest at sites of UV photoproducts, which have been shown to recruit components of the NHEJ system (87).

7. XERODERMA PIGMENTOSUM, COCKAYNE SYNDROME AND TRICHOTHIODYSTROPHY

7.1. Introduction

XP, CS and TTD are a suite of diseases with a common basis in the various pathways of NER (16). Several of the gene products are involved in multiple biochemical functions and protein-protein interactions such that the particular phenotype or clinical syndrome can be very variable according to the precise mutation and amino acid change in the protein (16). Although NER in its fullest involves up to 30 different proteins (36), only 8 have been associated with XP (complementation groups A through G and V), and 2 with CS (groups A and B) (36). The diseases are all rare autosomal recessive conditions that occur at a frequency of 1:250,000 (XP) or less in the United States (16).

7.2. Xeroderma pigmentosum

Homozygous XP patients show sun sensitivity resulting in erythema and increased freckling followed by progressive atrophy and telangiectasia in sun-exposed portions of the skin and eyes, usually leading to skin cancers of all kinds. Heterozygotes are generally asymptomatic. Some patients have, in addition, progressive neurological degeneration that can result in them expressing several symptoms characteristic of multiple syndromes, both XP and CS or XP and TTD. The median age of onset is 1-2 years of age, with skin rapidly taking on the appearance of that seen in individuals with many years of sun exposure. The SCC incidence is about 2000 times that seen in the general population under 20 years of age, with an approximate 30-year reduction in life span.

XP-A through G cells all show reduced excision of pyrimidine dimers and [6-4]PPs at rates that are 0 to 90% of normal. XP-V cells have normal NER, and lack the damage-specific polymerase Pol H. XP-A, D and G cells are very sensitive to killing by UV light and have negligible excision capacities for pyrimidine dimers and [6-4]PPs. XP group A cells also have a reduced capacity to repair the Dewar pyrimidinone, an important lesion produced by UVB conversion of [6-4]PPs (24, 111, 112). Other groups have intermediate NER capacities.

XP-A patients usually have a severe repair deficiency and exhibit both increased skin cancer and neurodegeneration, which is associated with mutations in the DNA binding regions of the gene (113). Some XP-A patients, however, have little neurodegeneration and mild symptoms, even in a Tunisian population who experience high sun exposure. These generally have at least one allele with mutations outside the DNA binding region (113, 114).

Group C is one of the largest groups and is often referred to as the common or classic form of XP. The patients show only skin disorders, which vary considerably in severity, depending on the solar exposure and tumors of the tongue have been observed in several patients (16). XP-C cells have low but heterogeneous levels of excision repair (10-20% of normal), and are less sensitive to killing by UV light and chemical carcinogens than cells in groups A and D. They can, however, still repair small regions of transcribed DNA at normal rates and are defective in repair of nontranscribed DNA (115). This implies that high rates of cell killing, somatic mutation, and cancer from UV light in XP group C are associated with unrepaired lesions in the nontranscribed regions of the genome or the nontranscribed strand of active genes.

Patients who are classified in XP groups B & D have the most complex clinical symptoms. Mutations in *XPB* and *XPD* give rise to a range of cancer and neurodegenerative diseases that often combine one or more of the three main disorders, XP, CS and TTD, depending in part on the precise site of the mutations in the genes. Additional complicating factors involving gene dosage also contribute to the syndromes observed. The genes are essential, being part of the basal transcription factor TFIIH (52), and patients usually need to express at least one allele with a missense mutation to be viable, and null alleles do not contribute to the clinical phenotype (116). Knockout mice in either gene are not viable and the embryos scarcely develop beyond a few cells.

XP-B is a rare group with only 5 patients known: 3 of these patients developed combined XP and CS disorders; 2 sibs had XP & TTD (117). The mutations all occur outside the DNA/DNA helicase domains (boxes I-VI) at either end of the gene.

XP-D encompasses a large heterogeneous group of patients that can exhibit combined symptoms of several diseases. These can be distinguished to a first approximation by whether mis-sense mutations occur within or outside the DNA/DNA or DNA/RNA helicase boxes (117) (Figure 2), since mutations that destroy the function of the protein do not contribute significantly to the clinical symptoms (116). The patients showing either XP or XP/CS symptoms generally show causative mutations that are in the DNA/DNA helicase box regions, whereas those showing TTD symptoms have causative mutations in the DNA/RNA helicase boxes (figure 2). This would reinforce the idea that XP and CS are predominantly repair disorders,

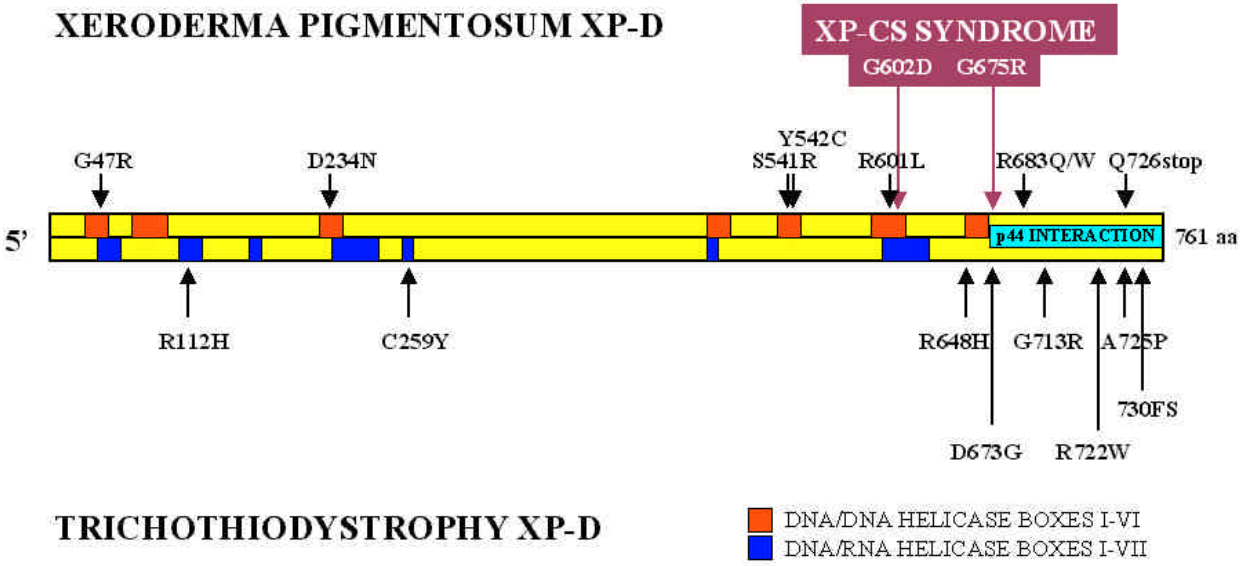

Figure 2. Causative mutations reported in the XPD gene after elimination of non-functional mutations. The DNA/DNA helicase boxes are shown by red boxes; DNA/RNA helicase boxes in blue boxes. Helicase boxes are given roman numerals starting from the 5' terminus. The mutations are indicated by the number and the type of amino acid change, with those causing XPD or XPD/CS above, and those causing XPD/TTD below. The interaction domain between XPD and the p44 component of the TFIIH complex is shown in light blue. Drawn from information provided by Drs A. Sarasin and P.H. Itin.

and TTD is a transcription disorder. Toward the 3' end of the XPD gene, between amino acids 650-761(end) this distinction is more difficult to make and the sites of mutations for different diseases are only separated by a few amino acids (117, 118).

XP group E patients have mild disease, and these cells show the least UV sensitivity and can excise UV damage at only slightly reduced rates. Despite some early uncertainty, the present view is that XPE patients and cells lack the p48 (DBB2) component of the p48/p125 damage-specific binding protein (119-122). The role of this protein is still unclear but it is involved in repair of nontranscribed regions of DNA and its expression is dependent on p53 (59, 60).

XPF patients have only been reported from Japan, and these have mutations in the XPF component of the XPF/ERCC1 5' endonuclease of excision repair (123). These patients generally have mild symptoms and the mutations in XPF result in decreased levels of the endonuclease activity and a resulting slow excision of photoproducts (124). Patients with mutations in ERCC1 have not been reported and knockout mice are born runted, with liver defects and die after a few weeks of life (64). The interaction sites between XPF and ERCC1 have been mapped and involve the C-terminal residues (814-905) of XPF and the C-terminal residues (224-297) of ERCC1 (124).

XPG patients generally show very severe symptoms of XP and XP/CS: developmental retardation, dwarfism, severe neurologic abnormalities, sun sensitivity and skin cancer. Only 10 patients are known in this group. The majority of these had NER that was less than 10% of normal and patients died in their first decade. XPG encodes an endonuclease that cleaves on the 3' side of an UV photoproduct, and which is also a cofactor that increases the activity of a glycosylase (endonuclease III, encoded by the nth gene) that acts on oxidative damage (61). Many of these severe XPG cases had mutations that truncate the XPG protein, but in one case a mild phenotype occurred in a patient who had a missense amino acid change in one allele and higher NER (125).

XPV patients resemble XPC patients (126) in having high risk for skin cancer but rare to no neurological abnormalities. They have normal NER but lack a DNA

polymerase, Pol H, that is required for accurate replication of pyrimidine dimers (81, 82). Most mutations in Pol H result in frameshifts and premature termination of the protein, but inactivating mis-sense mutations have been reported from *in vitro* experiments (74).

Consistent with the symptoms of XP patients, mice that lack XPA or XPC show increased UVB carcinogenesis (127, 128). XPA knockout mice however do not show the severe neurological disorders seen in XPA patients.

7.3. Cockayne syndrome

CS is an autosomal recessive disease characterized by cachectic dwarfism, retinopathy, microcephaly, deafness, neural defects, and retardation of growth and development after birth. They have a typical facial appearance with sunken eyes and a beaked nose and projecting jaw. CS patients are sun sensitive but do not develop cancers, setting this disease apart from XP. In addition to patients who show combined XP and XP/CS symptoms there are a set of patients who only have CS. These correspond to mutations in one of two genes, *CSA* and *CSB*, group A being the more common (129). Three patients from 2 families are known from XP complementation group B which also show CS symptoms (130). The CS gene products are involved in coupling excision repair to transcription, but their precise function is not yet clear. They may be involved in the ubiquitination and degradation of stalled RNA pol II at damaged sites.

Cockayne syndrome and XP group C make an interesting contrast. CS cells repair only transcriptionally inactive genes, whereas XP group C cells repair only transcriptionally active genes. They show a similar increase in sensitivity to cell killing, indicating that all regions of the genome must be repaired for normal survival. But only XP group C shows elevated mutagenesis and carcinogenesis. This comparison indicates that defective repair of transcriptionally inactive genes is more important for carcinogenesis in human cells and tissues. Interestingly, CSB knockout mice show elevated UV-induced cancer, even though CS patients do not, and their neurological symptoms are much milder (131).

7.4. Trichothiodystrophy

TTD is a rare autosomal recessive disorder characterized by sulfur-deficient brittle hair and ichthyosis (117). Hair shafts split longitudinally into small fibers, and this brittleness is associated with levels of cysteine/cystine in hair proteins that are 15 to 50% of those in normal individuals. The hair has characteristic “tiger-tail” banding visible under polarized light. The patients often have an unusual facial appearance, with protruding ears and a receding chin. Mental abilities range from low normal to severe retardation (132). Several categories of the disease can be recognized on the basis of cellular responses to UV damage and the affected gene. Severe cases have low NER and mutations in *XPB* or *D* as described above. A third category involves another unidentified gene called *TTDA* and lacks major UV sensitivity, and appears to have an unstable TFIIH (117, 133). Although TTD patients do not exhibit increased incidence of skin cancer, corresponding mice with a human TTD mutation are sensitive to increased UV-induced skin cancer, indicating important differences between the human and mouse models (134).

7.5. Other disorders involving NER genes

The spectrum of diseases associated with the NER gene family is far from exhausted. A recent association has been made of cerebro-oculo-facio-skeletal syndrome (COFS) with mutations in *CSB*, *XPG* and *XPD* (135). Testis cells and tumors are innately low in XPA, which contributes to their sensitivity to cis-Pt chemotherapy (136). Polymorphisms in several DNA repair enzymes have been reported in populations with increased susceptibility to malignacy (137). Tumors in general have extensive genomic rearrangements, amplifications and deletions, so it would not be surprising to find that derangement of DNA repair systems could be side effects of malignant progression.

8. SQUAMOUS CELL CARCINOMA

8.1. Clinical description and epidemiology

Nonmelanoma skin cancer (NMSC) has the highest incidence of any type of tumor in the world (2). In places such as Australia with a large light-skinned population and high solar exposure the cost to the health care system is extremely high (9). SCCs develop on the parts of the body which receive maximum UV exposure and exhibit chronic UV damage. The face, head, neck, backs of the hands and forearms are the predominant sites. Additionally, skin cancer incidence increases with age, suggesting that cumulative exposure is responsible for the development of these cancers (138). NMSCs arise from stem cells in the follicular and inter-follicular regions of the skin, but it is unknown whether SCC and BCC originate from different stem cells. SCCs arise from keratinocytes in the skin and lesions can be either confined to the cells in the epidermis, SCC *in-situ* or cancerous cells can radiate down into the dermis. Clinically the lesions present as an erythematous, indurated papule, plaque or nodule with adherent scale. When eroded or ulcerated the center may have a thick crust with a firm, indurated, elevated margin. The lesions may be single or multiple and occur on areas which have been exposed to the most solar UVB, including the scalp, face, ears, dorsum of the hands and forearms. The surrounding skin usually shows evidence of chronic sun exposure with telangiectasia, atrophy, excessive wrinkling and hyper- and hypopigmentation.

In addition to solar irradiation, other agents are known to cause SCCs, but whether the molecular progression is the same as for UVB is unclear. Epidemiological as well as experimental evidence has shown that arsenic exposure can cause skin cancer (139), which may develop through gene amplifications unlike other chemical carcinogens and UVB which induce gene mutations (140). The arsenical SCC develops in arsenical keratoses or areas of SCC in-situ. Arsenical keratoses are often seen on the palms and soles. After many years’ duration they may become painful, begin to bleed and ulcerate. The ulcerations will not spontaneously heal (3). Other experimental chemicals (e.g., DMBA) and tumor

promoters (e.g., TPA) have been extensively used to induce skin cancer in mice (141).

The carcinogenic potential of heat has been demonstrated by the practice of different cultures to place heated pots against the skin in order to keep warm, including Kasmir (kangri cancers), China (kang), Ireland (peat) and Japan (kairo) (3). The cancers develop in areas of chronic heat damage manifested clinically as reticulate pigmented brownish-red patches with telangiectases.

Carcinoma can also arise in skin damaged by x-rays, grenz rays or gamma rays. The first case of radiation-induced SCC was reported in 1902 when Frieben presented to the Physicians Society in Hamburg a man who used his hand as a test object in a roentgen tube factory. He developed a SCC on the back of his hand in the area of chronic radiation dermatitis (142, 143). A SCC developing in sites of radiation is potentially a dangerous tumor. It may appear as a scaling patch, erosion or ulceration. It can grow rapidly and some are among the most anaplastic carcinomas of the skin. Many times there are multiple tumors, which are often seen many years later on the face in people who were treated with x-rays as teens for acne. The dose response for ionizing radiation-induced SCCs shows a threshold, mainly because tumor development only occurs once significant pathological changes have occurred that alter the normal pattern of cell proliferation and exfoliation.

SCCs can arise in areas of chronic scars, ulcers and benign dermatoses including lesions of lupus eythematosus, lichen planus, porokeratosis, lichen sclerosus and epidermolysis bullosa. The scar SCC usually clinically appears as a new erosion or ulceration in a stable, longstanding scar. In chronic leg ulcers the inability to heal after meticulous wound care measures should arouse suspicion of an underlying cancer or infection.

Papillomaviruses are small DNA viruses that infect squamous epithelium leading to cell proliferation. Most commonly, infection by papillomaviruses causes warts, but they can cause other types of tumors and under the right conditions, malignant tumors. The papillomavirus infects basal cells but replicates in the fully differentiated keratinocytes. In certain high-risk HPV types this infection can progress from a benign papilloma to dysplasia and neoplasia. This occurs only with the cancer-associated types of HPV in certain predisposed individuals under the right environmental conditions. Under these conditions the HPV DNA is incorporated into the host's genome, with the loss of large regions of the virus's genome but retention of the E6 and E7 genes. The expression of both genes is critical for the oncogenic potential since E6 inactivates p53, a tumor suppressor gene, and E7 inactivates Rb which inhibits unregulated cell growth (144). The Buschke-Lowenstein tumor is a prime example, and is probably caused by HPV types 6 and 11. It is a locally invasive tumor that rarely metastasizes. It is considered to be a type of verrucous carcinoma (145, 146). This tumor clinically presents as a large cauliflower type mass on the genitalia. It is most common in uncircumcised men. It has a marked tendency to infiltrate deeply, causing local destruction of underlying structures.

The incidence of metastatic SCC has been reported to be as low as 0% and as high as 50%. This divergence is probably due to the selection of cases. There are however, certain characteristics, which if present, make a particular SCC more likely to metastasize. These include larger and deeper tumors as well as tumors of the lips, hands, and temples. Additionally, carcinoma invasive below the dermal sweat glands, or a tumor which is anaplastic, is more likely to metastasize (147). SCCs which develop from solar keratoses have a low rate of metastasis while those that develop after radiation treatment have a metastatic rate of 20-26% although variations in the rate of metastasis have been reported .

8.2. Molecular changes

The initial damage produced by solar UVB is eliminated from the skin either by NER or by proliferation and exfoliation from the skin's surface. Some cells in the skin also die by apoptosis following exposure ("sunburn cells") resulting in the elimination of damaged cells. A very low frequency of cells have been observed that appear to be quiescent and retain DNA damage for long periods seemingly without repair or proliferation (148). Stem cells for the epithelium are thought to reside in the bulge region of the hair follicles (149), but there are also secondary stem cells at the base of each column of epidermal transit amplifying cells in the epidermal proliferative units (150). The carcinogen-retaining cells may represent stem cells, or damaged cells with the potential to become mutants once stimulated to proliferate. The progression of molecular changes involved in SCC appears to be initiated by mutations in p53 that result in expanding clones in the sun-exposed areas of the skin that are initially confined within the proliferating units (151). These clones can be very frequent and can break out of the confines of the columnar structure of the proliferative units after chronic UVB irradiation (151). Most actinic keratoses and SCCs consequently represent clones that develop from cells that contain mutations in p53 that are characteristic of UV exposure, being in dypyrimidine sequences with notable frequencies of CC to TT changes (100, 152).

Subsequent to the expansion of p53 mutant clones additional factors come into play with other alterations in gene expression and copy number that have not yet been fully explored. Changes have been observed for example in EGF, *ras*, NFkb, JNK2, presenilin, MMP9, as well as various chromosomal regions identified by allelotyping that control tumor initiation and papilloma to carcinoma conversion (141, 153, 154). There may be an important role for the immune system in SCC formation since immune suppression in organ transplant patients enhances SCC formation, and the gamma-delta T cells negatively regulate tumor formation (155). The complete identification of all steps involved in SCC formation has yet to be made, but considerable detail is developing.

9. BASAL CELL CARCINOMAS AND BASAL CELL NEVUS SYNDROME

9.1. Clinical description and epidemiology

BCC is a malignant neoplasm that arises from the basal cells in the skin and the follicular infundibulum. It is the most common human cancer and occurs predominantly in fair-skinned individuals, affecting 750,000 Americans

per year. It is more common in males than females. Based on rapidly rising tumor incidence rates, it is estimated that almost one in three Caucasians born in the United States after 1994 will develop a BCC in their lifetime (156).

Clinically, BCCs can present as slowly growing pearly papules with overlying telangiectases. Other clinical presentations include poorly demarcated erythematous or a whitish, sclerotic plaque. Histologically, BCCs can be classified as superficial, nodular, infiltrative or morpheaform, depending on the configuration of the cells in the tumor. BCCs are relatively small (3 mm to 6 cm) tumors, have prominent vasculature visible by the unaided eye (a diagnostic hallmark), have a predilection for sun exposed skin (especially the face), and are epidemiologically linked to ultraviolet (UV) radiation, ionizing radiation, and arsenic exposure. The tumors are locally destructive, sometimes causing significant facial disfigurement, and almost never metastatic (< 0.1%).

BCCs develop most commonly on the face but in areas that are relatively sun protected including the inner canthus and behind the ears. Almost 1/3 of BCCs develop in sun-protected sites and unlike SCCs they are uncommonly found on the forearms or the backs of the hands. Recent data suggests that occupational and exposure late in life is important in the development of SCCs, while exposure during childhood and recreational exposure appears to be important in the development of BCCs (157). A history of intermittent exposure during childhood or adolescence, which resulted in severe sunburn, appears to increase ones risk of developing BCCs later in life (11, 12, 158-160). Thus, in terms of UV exposure the development of BCCs is more like melanoma, i.e., where early sun exposure appears to play a greater role than sun exposure in adulthood.

BCCs are of three histologic types distinguished by their architecture and amount of dermal invasion: the superficial BCC, the nodular BCC, and the infiltrative BCC. Common to all tumor types is a tumor cell that resembles the basal cells of the epidermis. Compared to epidermal basal cells, BCC cells have a large oval nucleus and relatively little cytoplasm (larger nuclear to cytoplasmic ratio). In BCC tumors the cell-to-cell boundaries are indistinct in contrast to the well-defined cell boundaries and intercellular bridges seen in epidermal basal cells. The superficial BCC is characterized by finger-like projections of tumor cell islands from the epidermis into the dermis. The tumor islands of superficial BCCs are attached to the epidermis and there is little penetration into the dermis. In contrast, nodular BCCs have tumor islands embedded in a fibroblastic stroma in the dermis and the tumor mass is principally in the dermis and not at the dermal-epidermal interface. In the infiltrative BCC, considered the most aggressive type, the tumor cells are arranged in strands a few cells thick. These strands can invade deeply into the dermis (161). The superficial BCC may progress to either the nodular or infiltrative tumor types. However, there is no evidence that all tumors pass through a superficial stage. Aggressive BCC tumors may invade deep into the dermal tissue, into cartilage and bone, and in approximately 1% of cases can invade along the outside of nerves known as perineural invasion. Perineural invasion is an indicator of high risk for recurrence.

The vast majority of BCCs appear sporadically but there are several heritable disorders in which affected patients develop BCCs at an earlier age and a higher rate than the general population. These include the basal cell nevus syndrome (BCNS), albinism, xeroderma pigmentosum, the Rombo syndrome and the Bazex syndrome (3). The basal cell nevus syndrome (BCNS) (162) is an autosomal dominant trait in which tumors begin at an earlier age (commonly in teenagers) and in which multiple independent tumors occur--typically dozens or even hundreds. Patients with BCNS often have not only BCCs but also a panoply of phenotypic abnormalities including jaw cysts, distinctive facies, palmar and/or plantar pits, and rib abnormalities. They also develop other tumors in abnormally high incidence. These include ovarian fibromas, mesenteric lymphatic cysts, medulloblastomas, meningiomas, and rhabdomyosarcomas (162). These patients are sensitive to x-rays.

9.2. Molecular changes

The defect in basal cell nevus syndrome appears to be in the human homolog of the Drosophilia gene *PATCHED* (*PTC)*. The gene is involved in embryonic patterning as well as determining the fate of multiple structures in the developing embryo. Both somatic mutations in sporadic BCCs and single allele mutations in patients with BCNS (163, 164), have provided strong evidence that this tumor suppressor is important in BCC tumorigenesis.

The patched protein (PTC) is a membrane receptor, and with the co-receptor membrane protein Smoothened (SMO), regulates signal transduction by the protein Hedgehog (hH) (165) (Figure 3). PTC, a transmembrane protein, functions as a repressor of the hedgehog signaling pathway in *Drosophila* and in mammals. PTC represses the pathway by inhibiting signaling by SMO (166, 167). SMO is released from PTC repression if (a) Hh binds to PTC, (b) PTC is mutationally inactivated, or (c) SMO mutation impedes PTC-SMO protein interaction (168). Once released from PTC repression, SMO signaling activates transcription factor Gli that in turn upregulates expression of *PTC* itself and of a variety of other genes depending on tissue, organism, and stage of development. Mutations in *SMO* have also been identified in BCCs and in these tumors, as in BCCs with *PTC* mutations, *in situ* studies detect increased *PTC* transcript in BCCs as compared to overlying epidermis and stroma (169, 170). Thus, *increased PTC* message levels correlate with *decreased* PTC protein function. The relevance of these *SMO* mutations is attested to by the development of BCCs in mice overexpressing mutant *SMO* (SMO^{mut}) and by transformation of REF52 cells with SMO^{mut} but not wild-type *SMO* + E1A (168). More than 50% of BCCs and 90% of SCCs also contain mutations in p53 with a specific signature induced by ultraviolet light and many other gene amplifications and deletions have been detected (171).

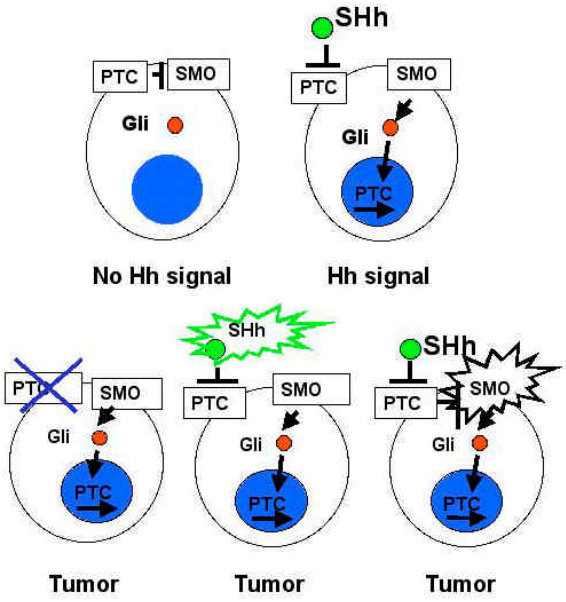

Figure 3. The mechanism of tumor formation in basal cell nevus syndrome involving the hedgehog (Hh), patched (PTC) and smoothened (SMO) signal transduction pathway. Top left: normal signal transduction pathway. PTC inhibits SMO and no nuclear transcription signal is induced. Top right: normal pathway after sonic Hh binds to PTC, removes binding to SMO, and results in signal transduction to nuclear transcription factor Gli that induces cPTC over-expression. Bottom: three mechanisms of derangement of the signal transduction pathways in tumors involving either PTC, SHh or SMO. Redrawn from initial diagrams provided by M. Aszterbaum MD, PhD.

10. MELANOMA

10.1. Clinical description and epidemiology

Melanoma develops from the malignant transformation of melanocytes located in the epidermis, dermis or mucosa. Of the three types of skin cancer melanoma is the rarest, but if not detected and treated early mortality rates are high. It is mainly a disease of Caucasians, but it does affect all races. The incidence of melanoma has been increasing worldwide over the last decade. In a study from the Saarland cancer registry from Germany melanoma age-standardized incidence rates increased 170% from 1970-1972 to 1994-1996 for men and 150% over the same period for women (172). A similar study showed that from 1979-1998, while melanoma incidence rose 132% in the US as a whole, the incidence in Wisconsin rose 25% over that time period (173). The reasons for the increased incidence of melanoma are varied and include increased UV exposure, changing leisure activities, change in clothing, environmental factors, and changes in the histologic criteria for diagnosing melanoma (3).

It is generally accepted that excessive sun exposure may predispose a susceptible individual to the development of melanoma. However, the link between UV exposure and melanoma is not as strong as in SCC where p53 mutations with an UV signature are seen (100). Additionally, it appears that intermittent exposure plays a greater role than chronic exposure. For example, the greatest increases in incidence of melanomas are seen on regions of the body where there is intermittent exposure: the lower extremities in women and the trunk in men (3). Severe sunburns in childhood or sun exposure in sunny locales during childhood also increases one's risk of melanoma (174, 175). Melanomas are also more common in light-skinned individuals, particularly those with red or blond hair who freckle easily (176, 177). Interestingly, it is now known that there is an association between the risk of developing melanoma and having specific mutations in the melanocortin-1 receptor (176). This receptor plays a key role in determining the type of melanin produced in melanocytes, eumelanin or pheomelanin. Loss of function of this receptor accounts for most of the red hair phenotypes seen in the human population, as well as individuals without red hair who have a decreased ability to tan. One of the stronger examples of a major role for UVB exposure in melanoma is the increased incidence of the disease in XP patients who cannot repair UVB damage (4). But even here, the distribution of melanomas over the body resembles that in the normal population and is not on the commonly exposed regions of the skin. Taken together these data suggest that UV does indeed play a role in the development of melanoma, although its exact role is not completely understood.

10.2. Molecular changes

Approximately 5-12% of patients who develop melanomas have one or more first-degree relatives with melanoma, suggestive of an autosomal dominant inheritance (178). Familial melanoma is, however, clinically and histologically indistinguishable from nonfamilial melanoma but there are differences in the age of diagnosis, lesion thickness and frequency of multiple lesions. Familial melanoma cases are generally diagnosed at an earlier age with thinner tumors and an increased frequency of multiple tumors (179, 180). There have been clusters of these cases, which may be due to chance, sharing of similar characteristics or the presence of a susceptibility gene (181).

There are two known melanoma predisposition genes, CDKN2A and CDK4 (178). CDKN2A is a located on the short arm of chromosome 9 (9p21) and functions as a tumor suppressor gene encoding two different proteins, p16 and p14arf (182, 183). The p16 protein is encoded from exons 1alpha, 2 and 3 of CDKN2A and functions as a cell cycle regulatory protein that inhibits the activity of cyclin D1 cyclin–dependent kinase 4 (CDK4) or 6 (CDK6) complex. This inhibition then acts as a negative regulator of growth by arresting cells at the G1 phase of the cell cycle. P14arf is formed from alternative reading frames. It acts via p53 to induce cell cycle arrest and apoptosis. CDK4 is found on the long arm of chromosome 12 (12q13). It seems to function as an oncogene that is resistant to the normal physiologic function of p16. Mutations in this gene are presumed to be very rare since co-segregating mutations have only been found in three melanoma-prone families (178). No clinical differences have been identified

between melanoma-prone families who have mutations in CDKN2A or in CDK4. The age at diagnosis, number of tumors and numbers of nevi are similar but this may change if more families are diagnosed with CDK4 mutations.

Comparative genome hybridization has identified a number of characteristic chromosome gains and losses in different classes of melanoma, and has especially aided in diagnosis of Spitz nevus, a benign melanoma of childhood (184). Spitz nevus can be difficult or impossible to distinguish from malignant melanoma in childhood by clinical and histopathologic examination. The majority of Spitz nevi have a normal chromosomal complement at the level of CGH resolution but some contain gains, with 11p being the most frequently involved location corresponding to amplification of the *HRAS* gene (185). Primary cutaneous melanoma shows a much more complex pattern of chromosomal gains and losses. These have frequent deletions of chromosomes 9p (82%), 10q (63%), 6q (28%), and 8p (22%), as well as gains of chromosomes 7 (50%), 8 (34%), 6p (28%), 1q (25%) by CGH analysis (186). Amplifications of chromosomal regions containing potential oncogenes were seen at 4q12, 5p14.3-pter, 7q33-qter, 8q12-13, 11q13.3-14.2, and 17q25. Losses of chromosomes 9 and 10 occur early in melanoma progression, whereas gains of chromosome 7 occur later. These findings suggest that the loss of chromosome 9p, the site of the p16 gene, is frequent in primary melanoma and occurs early in tumor progression.

The use of CGH and fluorescent in situ hybridization (FISH) has also enabled a molecular distinction to be made between acral melanoma (AM) that occurs on the palms of the hands and soles of the feet, and superficial spreading melanoma (SSM), the most common type of melanoma (187). All AMs had at least one (mean 2.0) gene amplification involving at least 15 different chromosomal regions, significantly more than the SSMs, in which only (13%) had a single amplification each. Comparison of the amplification levels of invasive and non-invasive portions of the tumors by FISH suggested that amplifications occurred before the formation of the invasive portion. Isolated melanocytes with amplifications in the epidermis could also be found up to 3 mm beyond the histologically recognizable extent of the melanomas.

The genomic changes in melanoma clearly are complex, although a general pattern has emerged of a major role for the p16 gene on chromosome 9p both in familial and sporadic melanoma. In addition, other genes may be involved including *PTEN*, and the p53, mdm2 pathway (187, 188).

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