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DNA Damage and Repair in Melanoma

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Abstract

Bulky DNA adducts are formed by UV irradiation in melanoma. If these adducts are not repaired, they can lead to the formation of mutations that may contribute to tumour growth and progression. UV-induced damage is uniform throughout the human genome but formation and repair of UV-induced DNA damage in human cells are affected by cellular context. Mapping bulky adduct (CPDs and 6-4 photoproducts) damage from UV irradiated cellular and naked DNA revealed that accommodating the binding of proteins involved in transcription, regulation, replication and repair may induce conformational changes in the DNA making the region either more or less susceptible to the formation of bulky DNA adducts and affecting repair efficiency at DNA binding sites. The effect of transcription factor binding on bulky adducts varies, depending on the specific transcription factor, damage type and strand. On the other hand, repair is affected by chromatin states, transcription, and transcription factor binding, depending on the type of DNA damage.

1. Introduction: The Structure of DNA, Chromatin and the Nucleosome

The double stranded helical structure of DNA with two rows of deoxyribose backbones running in opposite directions but rotating about each other separated by intervening base pairs is familiar. What may not be immediately appreciated is that DNA has a recurring pattern of alternating grooves, not of equal size to each other, a consequence of the geometry of the base pairs. The angle at which the two sugars protrude out from the base pairs, i.e. the angle between the glycoside bonds, that link the bases to the backbone, is either 240° or 120° and is responsible for these major and minor grooves, creating a pattern of regular, repetitive structural variation.

The base pairs sit with their ring structures stacked on top of each other perpendicular to the run of the backbone of deoxyribose structures on either side. The narrow angle between the sugars on one edge of the base pair generates a minor groove and the larger one on the other edge generating the major groove.

Human chromatin is a complex of DNA and protein, packaging the long strand of DNA molecules into more compact, denser structures to enable it to fit within the confines of the nucleus. This comes in two forms, euchromatin- lightly packed, enriched in genes and available for transcription (92% of the genome), and heterochromatin- tightly packed and less accessible. Euchromatin is the only form of chromatin in prokaryotes indicating that the heterochromatin structure evolved later, along with the nucleus, as a mechanism to deal with increased genomic size. This packaging is assisted by the formation of nucleosomes. A histone octamer, with the strand of DNA wrapped twice around it. Euchromatin is regulated by post-translational modification. This occurs on N-terminal histone tails that protrude from the nucleosome structure. They recruit enzymes that either open or close the structure. Histone methylation is associated with heterochromatin and acetylation is associated with euchromatin where a more negative charge disrupts its interaction with the DNA strand. Chromatin can also be modified by phosphorylation controlled by kinases and phosphatases, occurring at serine, threonine or tyrosine residues present on euchromatin.

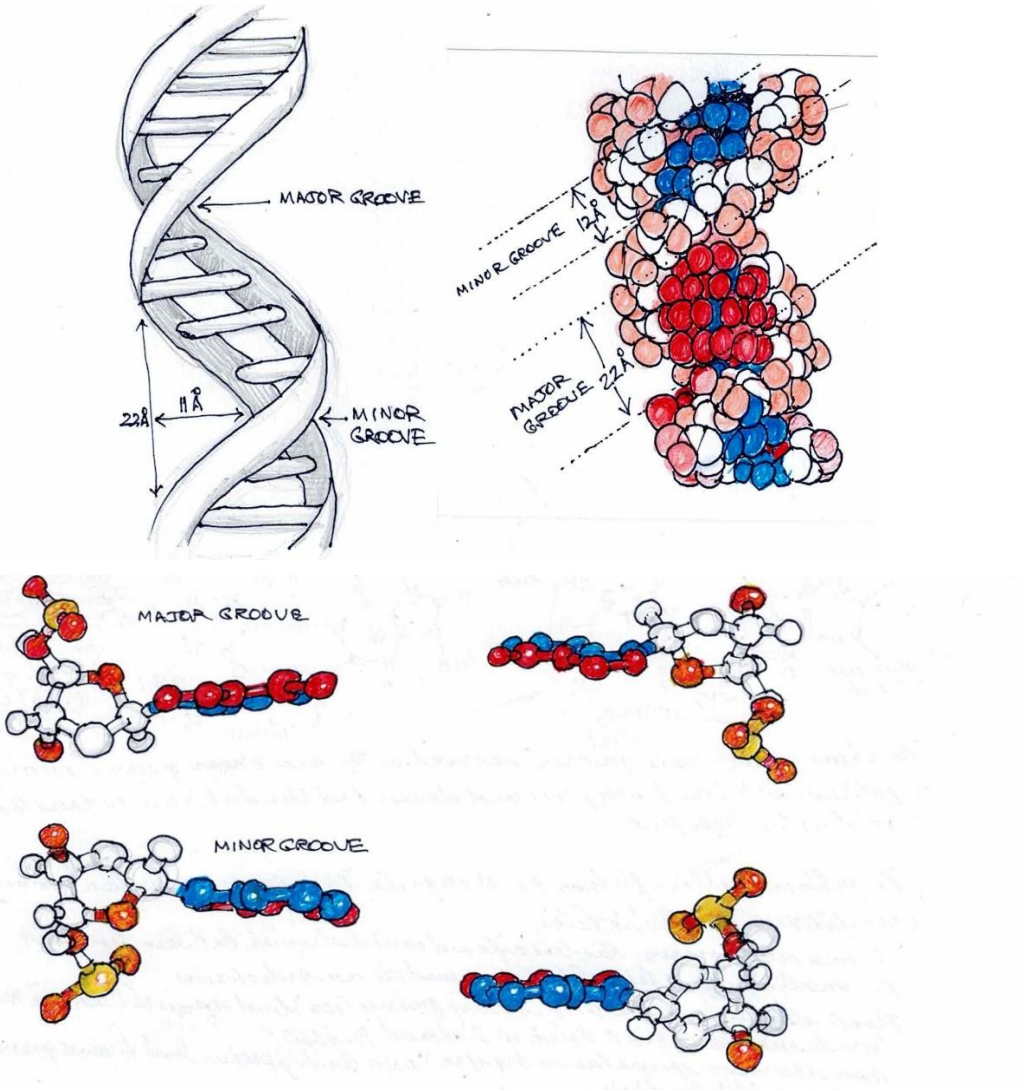

FIG. 1. **The structure of DNA.**

The DNA molecule twists to form a double helix with the base pairs stacked between the two strands. The two parallel sugar-phosphate backbones on each side of the helix are not directly opposite each other. This uneven arrangement creates two grooves. A wider major groove and a narrower minor groove.

In the diagrams the nuclear based atoms facing the major groove are coloured red and those facing the minor groove are coloured blue.

Looking at the left backbone, the deoxyribose points the ring oxygen up with the phosphate group at the top when facing the major groove, whereas it points down when facing the minor groove. This arrangement is complementary to the right backbone which has the opposite orientation. This arrangement can be understood if it is appreciated that the backbones are travelling in opposite directions.

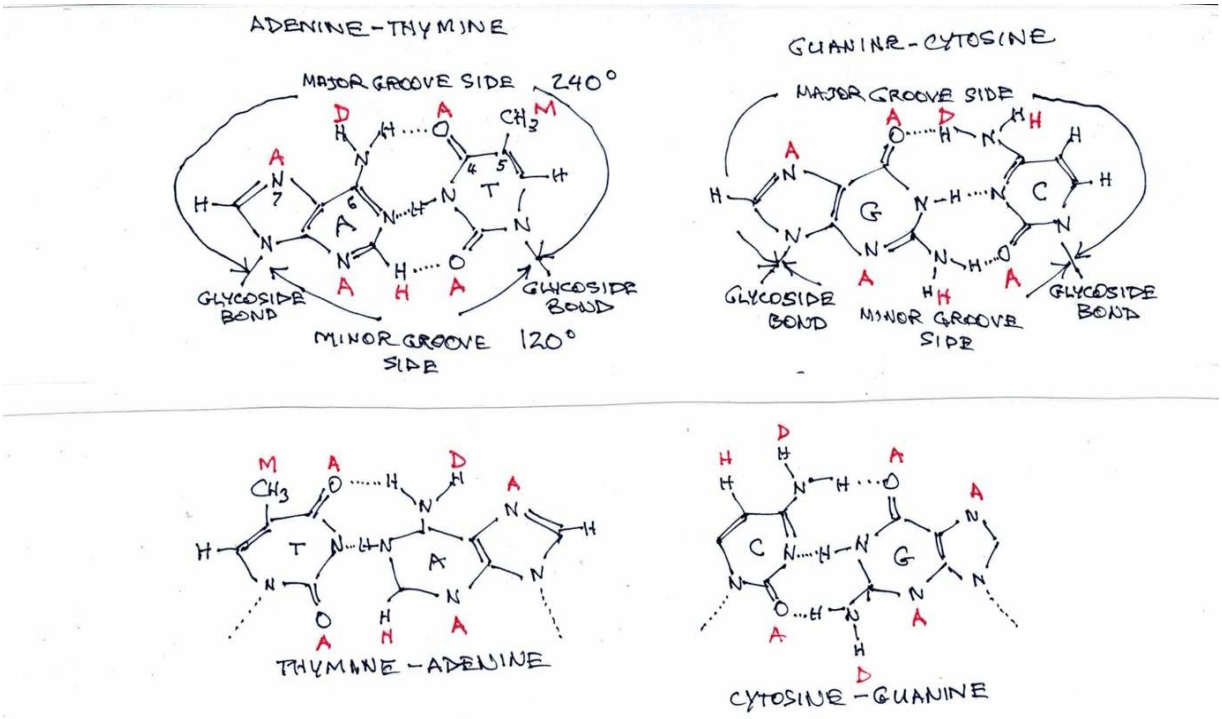

FIG. 2. **The uneven sides of the base pairs create the minor and major grooves.**

There are characteristic patterns of hydrogen bonding and of overall shape that are exposed in the major groove that distinguish an A:T base pair from a G:C, also A:T from T:A and C:G from G:C. E.g. Structures exposed on the major groove side at the edge of an A:T pair-a hydrogen bond acceptor (A), N7 of adenine; a hydrogen bond donor (D), the exocyclic group on C6 of adenine; a hydrogen bond acceptor (A), the carbonyl group on C4 of thymine; a bulky hydrophobic surface (M), the methyl group on C5 of thymine. This creates the code 'ADAM'. Thus, the code 'ADAM' distinguishes the A:T base pair from the 'MADA' code of the T:A base pair, similarly for G:C and C:G base pairs. The base pairs cannot be distinguished from the minor groove side which has the invariable 'ATA' code for all base pairs. The major groove side contains more chemical information and larger size for identification and accommodation by proteins side chains. Most sequence specific DNA binding

proteins, transcription factors, regulatory, replication and repair proteins, bind via the major groove. Non sequence specific DNA binding proteins, histones, ribosomes and DNA polymerases mainly bind to the minor groove and may unwind and bend the DNA. Their smaller size is also less able to accommodate amino side chains.

2. Formation of Bulky DNA Adducts

UV irradiation is the primary aetiological agent for melanoma, inducing carcinogenic lesions in DNA. The primary lesion induced by UV is the cyclobutane pyrimidine dimer (CPD) at dipyrimidine sequences, which comprises approximately 80% of UV damage to DNA [1]. Pyrimidine 6-4 primidone photoproducts (6-4 PPs) are also involved but to a lesser extent. CPDs are formed by a cycloaddition reaction when a cyclobutane ring develops between the C5 and C6 positions of two adjacent pyrimidine bases resulting in a covalent cross-link. 6-4 PPs are formed by a single covalent bond between the C6 of the 5' end and the C4 position of the 2' end of two adjacent pyrimidine bases. These helix-distorting DNA lesions within the local DNA double helix (CPDs produce a 9° bend and 6-4PPs a 44° bend) are an obstruction to polymerases and error-prone bypass of CPD lesions during replication is thought to be the primary cause of UV-induced mutations in melanoma [2]. However, formation frequencies are strongly dependent on DNA sequence context, and the quantum yield is low because the distance between and alignment of neighbouring C5-6 double bonds is unfavourable to cycloaddition in canonical B-form DNA.

CPDs form, in part, from fluctuations in canonical DNA structure, transient conformational changes leading to more favourable distances and alignment parameters for CPD formation upon UV absorption. Alterations in DNA conformation or mobility has also been found to be influenced by a number of other factors. DNA-bound proteins affect the rate of CPD formation and CPD formation is significantly modified by packing of DNA into chromatin, the primary building block of which is the nucleosome. This has approximately 147 base pairs (bp) wrapped twice around an octamer of histone proteins [3]. The DNA is strongly bent as it wraps around the histone complex, particularly at every 10th bp where the DNA minor groove faces the octamer [3-6]. The histones directly contact the sugar-phosphate backbone of the DNA at these minor-in rotational settlings, resulting in constrained DNA mobility and sharp-bending into the minor groove through alterations in the roll and slide parameters of the DNA base stack [3,4]. CPD formation is suppressed at minor-ins but elevated at minor-out positions, where the DNA minor grove faces away from the octamer [7-12] (FIG. 3).

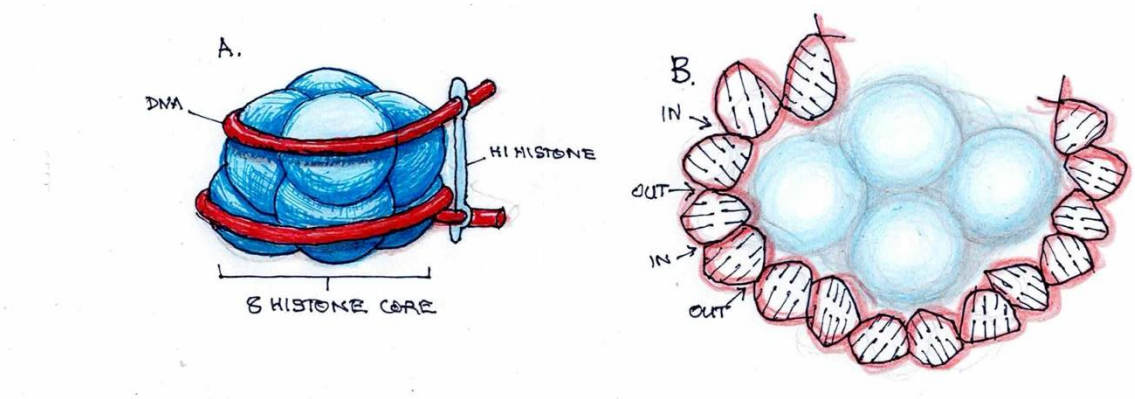

FIG. 3. **Nucleosome structure**. **A. DNA wrapped twice around the histone octamer (side view) B. Different bending parameters at minor-ins and minor-outs (top view).**

It has been shown that other DNA-bound proteins, including transcription factors also significantly modulate CPD formation at their DNA binding sites [13-17]. In particular, It was found that for both CCCTC-binding factor (CTCF), a highly conserved zinc finger protein involved in organisation of DNA into a 3D genomic structure and acting as a transcription factor activating or repressing gene expression, and members of the E26 transcription specific (ETS) family, were responsible for binding-associated changes with a decrease in the distance and relative torsion angle of the C_5-C_6 atoms of neighbouring pyrimidines, an explanation for the observed UV damage and resulting CPD induction at their binding sites. These structural changes regulating the frequency of CPD formation.

Stark et al specifically investigated DNA conformational changes. Their findings revealed that periodic changes in conformation of nucleosomal DNA as it bends around the histone octamer modulates susceptibility to UV damage. Their analysis indicated that the distance and torsion angle between the CPD forming C5-6 double bonds of neighbouring pyrimidines showed favourable values at minor-out rotational settings and unfavourable values at minor-in positions. Structural parameters strongly correlating with CPD enrichment in the nucleosomes from UV-irradiated cells [18] (FIG. 4).

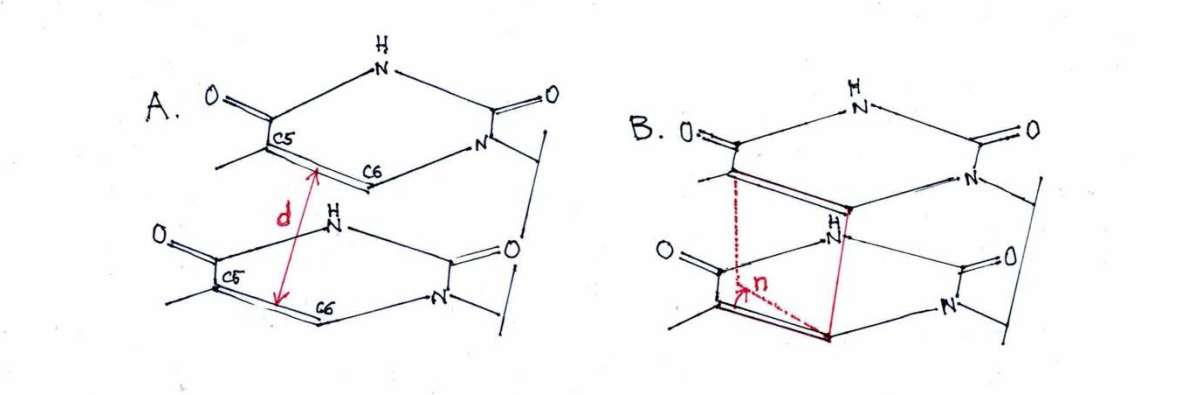

FIG. 4. **Distance and torsion angle of C5-C6 double bonds of neighbouring pyrimidines. A. Distance measurement (d) made between the midpoints of the C5-C6 double bonds of adjacent pyrimidines. B. The improper torsion angle (n) made for the 5' C5-C6 and 3' C5-C6 double bonds of adjacent pyrimidines in nucleosome structures.**

3. Mutation Formation Vs Repair Efficiency

Mutation frequency across the genome in cancers is not evenly distributed. It is significantly increased in heterochromatin with increased UV lesion susceptibility and decreased repair in heterochromatin Vs euchromatin. In melanoma, however, mutation susceptibility and repair are not always inversely proportional. There are mechanisms of negative selection in these regions essential for cell viability, immune function and induction of apoptosis when mutated.

The presence of bulky UV lesions can interfere with transcription and replication potentially compromising genome stability and cell viability. NER machinery is utilised by the cell to remove adducts utilising two distinct sub-pathways. Global genome NER (GG-NER) probes the genome for bulky DNA lesions, whereas transcription coupled NER (TC-NER) activates when lesions stall RNA polymerase during elongation. Greater distortion caused by 6-4 PPs are recognised by GG-NER and generally repaired with greater efficiency than CPDs. CPDs with lesser distortion are recognised on the template strand by TC-NER.

C>T mutations are the UV signature mutation at dipyrimidine sequences and are the most prevalent mutation in cutaneous melanoma. Melanoma having one of the highest somatic mutational loads of any cancer, making it difficult to determine the relative mutagenic contributions.

UV-induced mutations result from the complex interplay between DNA damage, inadequate repair and replication errors occurring within a dynamic chromatin landscape. Chromatin has an important role in regulating gene expression and maintaining genome integrity by organising the genome into structurally and functionally distinct eu- and heterochromatin compartments. Heterochromatin, enriched for trimethylated histone H3 lysine 9, are highly compacted regions with elevated somatic mutation frequency [19,20]. NER is more active in gene rich euchromatin regions, whereas heterochromatin is the region of lower repair [21,22].

DNA sequence is an important factor in UV lesion formation, but nucleosomes and other DNA binding proteins also modulate lesion formation [11]. CPD distribution display an ~10 bp periodicity within nucleosomal DNA but are randomly distributed in linker regions, however 6-4 PPs are more frequent here. The “bodyguard hypothesis” proposed by Hsu in 1975 suggested that heterochromatin located at the nuclear periphery protects gene-rich euchromatin located in the interior [23].

Mutagenic potential is contributed by both UV susceptibility and repair, but susceptibility may largely influence mutation rates. Perez et al identified several oncogenes and tumour suppressors with high mutagenic potential (susceptibility/repair ratio), *NRAS, PTEN, NF1, ARID2* and *VHL*. Enhancers of several tumour suppressors were also found to have higher mutagenic potential, *TP53, NF1* and *VHL*, revealing that many cancer driver genes are predisposed to mutation by being in genomic regions with relatively higher susceptibility and lower repair [24].

Enhancers of genes involved in essential cellular component such as ribosomes and mitochondria were identified as more susceptible to 6-4PPs than CPDs. 6-4PP damage observed to trigger apoptosis, whereas CPDs induce cell cycle arrest [25,26]. This apoptosis could contribute to negative selection in a tumour population. Apoptosis plays a role in skin aging [27], suggesting an additional role for 6-4PPs in photoaging.

Immune-related signalling pathways and structural components localised to the cell periphery were enriched in regions more susceptible to 6-4PPs than CPDs, identified as targets of negative selection in melanoma [28,29]. Mutations may lead to the development of major histocompatibility complex (MHC) neoantigens, proposed to facilitate immune evasion of cancer cells from host immune surveillance [28]. There are interesting parallels between mutagenic potential associated with UV-induced damage and other carcinogens, potentially revealing evolutionary conserved processes for tolerance of environmental genotoxins [24].

4. Transcription Factor Influence on Nucleotide Excision Repair

There is a close relationship between TFs, NER and cancer-related pathways. TFs are involved in either oncogenic or antioncogenic pathways. Depending on the mutational or transcriptional status of TFs, cellular proliferation, differentiation or migratory characteristics may be altered. Different TF binding motifs affect NER activity and damage formation, shaping the

mutational landscape at their motif with a determinant role of impaired repair in the observed increase in mutation rate [17]. TP53, c-Fos, CLOCK-BMAL 1, Sp1 and HIFIα are some of the proteins shown to be involved in regulation of NER genes in mammals [30]. Regulation of the expression of NER genes is affected by UV but is also under the control of other mechanisms such as the circadian clock and hypoxia. Kang et al reporting that in the mouse brain XPA expression oscillated with the circadian rhythm, finding higher NER activity in the evening but lower at night and early morning [31]. TFs tumour protein (TF 53) and activating protein (AP-1) regulate genomic stress response through modulating NER gene expression [32].

5. The Role of Transcription Factor Binding on UV-Induced Damage

Mao et al initially showed that not only nucleosome structure but also TF binding affects DNA adduct formation in yeast [33]. It was then demonstrated that CPDs are enriched at active TF binding sites involving erythroblast transformation specific (ETS) binding motifs, which corelated with the mutational landscape of melanoma [14]. Binding sites of the ETS.TF family have been reported to being the most sensitive to UV-induced damage [34]. ETS binding motifs were enriched in CPD lesions with some coinciding with somatic melanoma mutation hotspots [35]. Sivapragasam et al, in UV-exposed cells, observed low CPD damage on CTCF binding sites but hotspots for CPD damage on certain positions of the motif, coinciding with hotspot mutations of melanoma. They showed that CTCF interacts with binding sites containing UV damage and inhibits repair [13].

6. CTCF Binding Modulates UV Damage

Somatic mutations are elevated at DNA binding sites of CTCF insulator protein in many cancers. These mutations are clustered at a particular hot spot of the CTCF-binding motif in melanoma. This is a conserved CC dinucleotide at the 5’ end of a cytosine-rich strand of the CTCF-binding site (CBS). i.e. position -4/-3 relative to the motif midpoint. Investigation found that although decreased NER activity occurs generally across the CTCF-binding motif it is not specifically associated with the 5’ mutation hot spot. Their data indicated that the CTCF binding induces mutation by promotion of UV-induced CPDs rather than differential NER inhibition [13].

7. DNA Adducts, Nucleotide Excision Repair and Transcription Factors in the Melanoma Mutational Landscape

Somatic mutations are unevenly distributed throughout the genome matching the distribution of DNA adducts [8]. Elevated CPDs coincide with mutational periodicity in nucleosomes where repair activity is low, demonstrating that unrepaired CPD damage is the source of somatic mutations in melanoma [11]. DNA binding proteins behave like an obstacle for recruitment of NER proteins in the presence of UV-induced DNA adducts initiating the formation of somatic mutations [36]. Late repair of UV-induced DNA adducts reported to be associated with cancer related mutations in melanoma [22]. Cytosine deamination of CPDs was detected upstream of transcription start sites, indicating TF binding sites, coinciding with UV signature mutations in melanoma [37]. There was found to be mutation accumulation at ETS.TF’s binding sites, especially promoters, coinciding with UV-induced CPDs [15] potentially regulating gene expression. The question remains- do these mutations prioritise cancer related genes?

Higher mutation rates on ETS binding motifs are mostly at the 5' end cytosine, suggesting that they are formed due to unrepaired CPDs. Similarly, CTCF binding motifs coincide with hot spot mutations in melanoma [13]. Studies of TERT promoter mutations showed that canonical mutations on the promoter leads to the formation of de-novo ETS motifs, making these regions susceptible to UV damage [38]. Evidence that, under certain conditions, the formation of mutations can influence UV susceptibility of a region. In conclusion, mutation susceptibility at TF binding sites results from a combination of susceptibility to DNA adduct formation combined with the level of efficiency of NER at these sites.

8. Conclusion

Melanoma carries germline variants in their inherited genome as well as somatic sequence variants. Although coding regions have received most attention and protein-coding genes such as DNA repair and cell cycle genes are important in tumorigenesis, most variants, both somatic and germline, occur in non-coding portions of the genome with many loci associated with cancer susceptibility. There is also a diversity of mutational types from single nucleotide variants to large genomic rearrangements. Somatic mutational frequency varies considerably across different cancer types, as do the proportion of coding to non-coding mutations. The challenge is to identify the driver from the multitude of passenger mutations, particularly with melanoma having consistently higher levels of mutation than all other tumours.

A range of somatic signature mutations have been identified, often shared across cancer types but the UV signature is specific to melanoma. Non-coding elements have diverse roles in the regulation of protein-coding genes but can mostly be considered as cis-regulatory regions. This includes promoters, enhancers and insulators, which regulate gene expression following binding by TFs to specific DNA sequences in regions of non-nucleosomal chromatin. Distal regulatory elements may regulate gene expression by creating loops that allow interaction with promoters, adding an extra layer of complexity to the 3D structure of the genome and crucial to understanding the effects of sequence variants.

Despite the complexity of DNA damage and repair the main mutagenic factor is simply exposure to UV light. So, why should melanoma have emerged as an increasingly significant health issue amongst Caucasian populations only over the last century considering that man has been exposed to this carcinogen since the beginning of time? Prevention basically requires sensible sun exposure, but this seems to pose problems for urban populations that spend extended periods in-doors under artificial light. Indigenous populations generally have more regularity with exposure that allows for adaptation through tanning and heavier constitutional pigmentation providing a more protective effect. Due to varying levels of dysfunction of the melanocortin receptor (MC1R) on the melanocytes of fairer skinned Caucasians the tanning response is incomplete, and this cannot provide adequate protect without addition of clothing, hats and sunscreen.

A delicate balance is maintained between protection of the structure and mechanism of the genome against the necessity for adaptation. The system needs consistency in reproducibility. Within this system there remains the possibility of mutations. These mutations may have deleterious effects but may also leave the door slightly ajar providing the opportunity for evolution and the application of survival of the fittest within a changing environment.

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