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The Role of Non-Coding Driver Mutations in Melanoma: A Review

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Abstract

Melanoma formation involves random mutational events with positive evolutionary selection acting on some of these events to produce driver mutations. Looking for these driver mutations in DNA initially focused on protein-coding somatic mutations. However, the availability of whole genome analysis has broadened the scope of enquiry to include potential driver mutations in non-coding regions of DNA. Mutations are abundant in this non-coding space, 50 times larger than the coding exome. Despite the number of events and size of the space, non-coding driver events appear relatively infrequently, and this is complicated by the difficulties of identifying signals of positive selection. Although rare, certain mutations occur outside the commonly targeted mutations and are more frequent in specific melanoma subsets, potentially offering therapeutic value. Beyond therapeutic application, these investigations increase our understanding of the mechanisms and complexity of DNA function and disruptive effects of mutation.

1. Synonymous Vs Non-Synonymous Mutations

Synonymous mutations change DNA but not the resulting amino acid sequence that codes for a protein. Non-synonymous mutations alter the coded protein. Synonymous mutations occur within coding regions (exons) but don't change the protein structure whereas, non-coding mutations happen outside protein coding genes (introns), affecting regulatory elements. Both types can impact gene expression and function, with synonymous mutations sometimes affecting mRNA stability or translation efficiency. Non-synonymous mutations increase diversity within the gene pool for natural selection to work on and drive evolution on a micro-evolutionary level.

2. Introduction

Until recently most sequencing studies relied on analysis of exomes, identifying a spectrum of driver genes with recurrent protein-coding somatic mutations, establishing a framework for genomic classification of melanoma. *BRAF, NRAS, NF1* mutations and triple wild type. However, in 2013 it was demonstrated that the known cancer gene *TERT* can be transcriptionally activated by somatic point mutations at two positions in the promoter, which induce new transcription factor binding sites. Around the same time there was shift from examining protein-coding somatic changes to whole genome sequencing of tumours. This enabled the search for additional non-coding driver mutations culminating in the publication of the Pan-Cancer Analysis of Whole Genomes (PCAWG) papers, which analysed more than 2600 genomes [1]. Examination of these genomes was then undertaken looking for signals of positive selection in non-coding DNA, which might represent driver events contributing to tumour development. Unfortunately, beyond *TERT* few were found and they exhibited a low rate of recurrence [2].

Driver gene activity in cancer is often altered by transcriptional activity or inactivity as in DNA copy number changes or promoter methylation events affecting oncogenes or tumour suppressors [3]. Non-coding point mutations may contribute through changes in enhancer sequences [4], altering gene expression through disruption of chromatin domain structures [5], 5' or 3' untranslated region alterations affecting mRNA stability or protein translation [6], and mutations in non-coding regulatory RNAs [7,8].

At the single base level, mutational probability is strongly influenced by the immediate tri-nucleotide sequence context, as shown by studies of mutational processes and their sequence characteristics [9]. Specifically, in melanoma mutations occur preferentially in TC, CT and CC containing contexts, reflecting the influence of UV radiation and the cyclobutene pyrimidine dimer (CPD), the main UV-induced DNA damage lesion [10].

The impact of localised mutational effect on the landscape is illustrated by cutaneous melanoma, which is dominated by promoter mutation hot spots, specifically ETS transcription factor (TF) binding sites. These ETS transcription factors are a large family of proteins that control gene expression by binding to specific DNA sequences. Elliott et al exposed cultured melanoma cells to UV light. Sequencing revealed a raised susceptibility to UV-induced mutagenesis at these positions [11], thought to be attributable to ETS proteins changing the local DNA geometry facilitating CPD formation, independent of DNA repair [12]. Although NER is inhibited at binding sites, modifying ETS and CTCF insulator proteins. CTCF is a multi-zinc finger protein acting as a boundary marker, responsible for organising 3-D genome architecture, regulating gene expression.

Most mutations in cancer are passengers that provide no clonal growth advantage. However, the large size of the human genome and the high mutational burden in melanoma means that passenger mutations in functional non-coding elements are expected to be frequent, sometimes with measurable molecular effects. The challenge, as with protein-coding DNA, is to identify signals of positive selection. The major source of mutation rate variability is differential DNA repair, particularly mis match repair and NER in cutaneous melanoma [13-16].

90% of melanomas arise on intermittently or chronically sun exposed skin, classified as superficial spreading, lentigo maligna and nodular subtypes [17]. The next most common is uveal melanoma, occurring in pigmented areas of the eye and partially related to UV exposure [18]. Less common again are types on non-sun-exposed areas, acral lentiginous and mucosal. Even

though uncommon these subtypes are all aggressive once they metastasise and respond poorly to currently available therapy [19]. Nearly 50% of patients with cutaneous melanoma have activating mutations in *BRAF* that can be targeted with specific inhibitors or its downstream kinase MEK (a member of the MAPK signalling cascade that is active in melanoma). However, this mutation is less common in other melanoma subtypes. Other oncogenic driver mutations in genes such as *NRAS, KIT, GNAQ* and *GNA11* have been identified in these subtypes but at a much lower frequency [20]. Approximately 25% of cutaneous melanoma and 40%-50% of non-cutaneous melanoma lack the common driver mutations and have no targeted therapy options available [21].

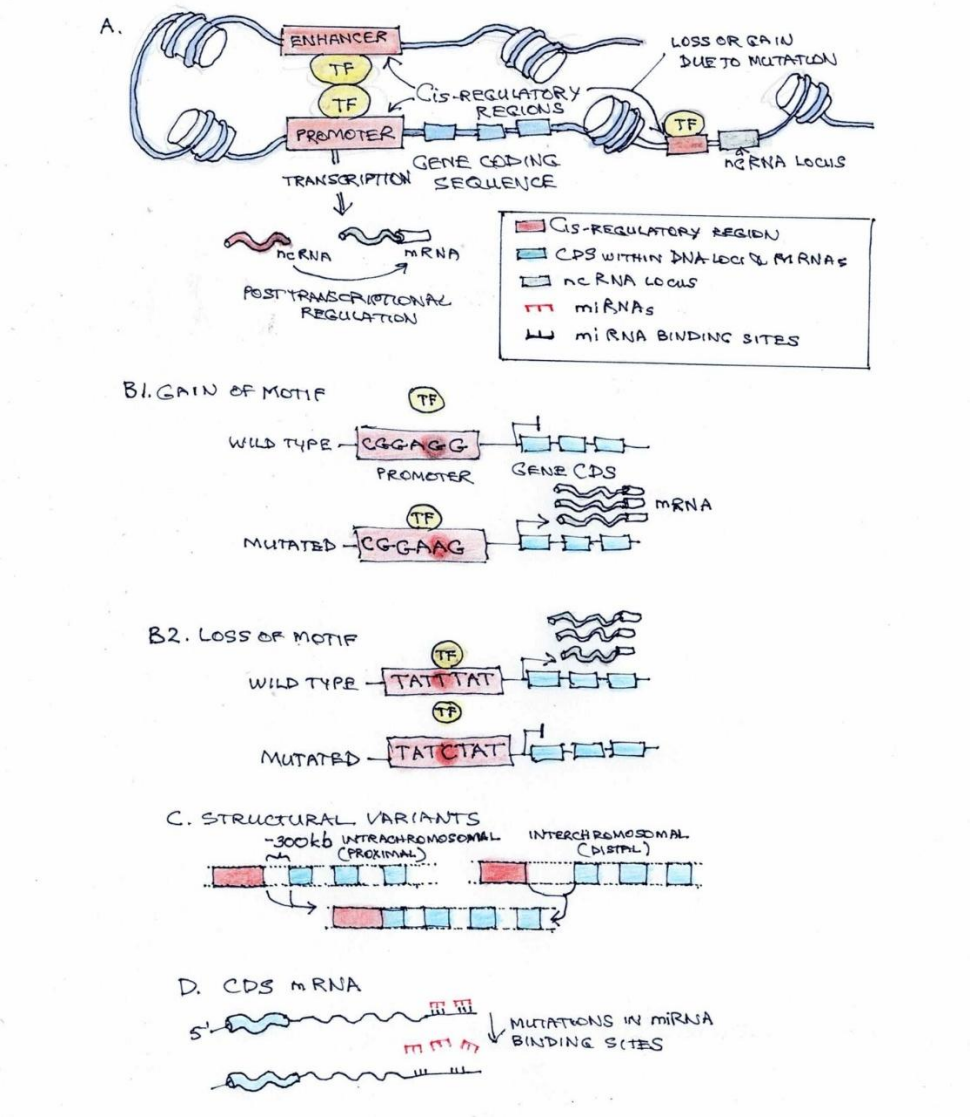

FIG. 1. **Effects of sequence variation in non-coding regions in tumorigenesis.**

Mutations can lead to gain or loss of TF binding motifs. Other sequence variants, such as amplification or deletion of the motif can have the same effect. **A.** Non-coding elements that can be affected. **B1.** Mutations that can lead to gain of TF-binding sites. **B2.** Mutations that can lead to loss of TF-binding sites. **C.** Structural variants can juxtapose the oncogene next to the regulatory element. Other structural variants can juxtapose the gene next to the enhancer, leading to its transcription. **D.** Mutations in

micro-RNA (miRNA) binding sites prevent miRNA binding, leading to increased target gene expression. (Modified from Khurana et al [35]).

3. *TERT*- An Example of Gain of Transcription Factor Binding Sites

Cell division causes shortening of telomeres, which are repetitive sequences at the ends of chromosomes, eventually leading to replicative senescence, the Hayfield phenomenon [22]. To avoid this, cancer cells activate telomerase, a protein-RNA complex that maintains telomer length, normally active in stem cells and other cells with a high self-renewal rate but inactive in most differentiated cells [23]. This is achieved through transcriptional activation of *telomerase reverse transcriptase* (*TERT*), the gene that encodes the catalytic subunit of the enzyme telomerase [24]. Telomerase lengthens telomeres, allowing cells to escape apoptosis and become cancerous. *TERT* expression is generally repressed in normal somatic cells but can be overexpressed in cancer cells [25]. Numerous studies have reported recurrent mutations in the TERT promoter in many cancer types. These mutations create binding motifs for the ETS family of transcription factors (TFs) leading to TERT promoter and subsequent up regulation of gene expression. Tumours with relatively low rates of self-renewal such as melanoma tend to exhibit higher frequency of TERT promoter mutation [26]. The high occurrence of these mutations' points to their role as driver mutations.

Huang et al investigated the highly recurrent TERT promoter mutations in melanoma. They describe two independent mutations within the TERT promoter occurring in 71% of melanomas examined. These mutations generate de novo consensus binding motifs for E26 (ETS) TFs increasing transcriptional activity for the promoter by X2-4. They showed that these promoter mutations occur almost exclusively at cytosines flanked by a distinct sequence signature TTCCG. In active (but not inactive) promoters' mutational frequency for cytosines at the 5' end of the ETS-like motif was higher than expected based on UV trinucleotide mutational signature. This sequence indicates an exceptional local vulnerability to UV-induced mutagenesis [27].

4. Loss of Binding Sites

In melanoma, the loss of TF binding sites is through recurrent non-coding mutations, single nucleotide or genomic rearrangements, that disrupt regulatory motifs. While some mutations create new binding sites e.g. TERT promoter mutations, others specifically abolish them to downgrade tumour suppressors.

There are two mechanisms responsible for loss of binding sites. Firstly, UV-induced hypermobility: Binding of TFs, like ETS, to DNA can increase local susceptibility of UV damage. This structural distortion creates mutation hotspots where the binding site is lost over time. Secondly, Impaired repair: The presence of a bound protein can block access to the nucleotide excision repair (NER) machinery preventing repair of UV-induced lesions at specific sites, making it more likely that the mutation will permanently disrupt the binding motif.

5. SDHD Promoter Mutations

The *SDHD* gene encodes the subunit D of the succinate dehydrogenase complex, an integral membrane protein. Recurrent mutations occur almost exclusively in melanoma, at a frequency of 4%-5% [28,29]. These variants are anticipated to disrupt consensus ETS transcription factor binding sites, resulting in reduced binding of GABPA and GABPB1, decreasing *SDHD*

gene expression and associated with a poor prognosis [30]. SDHD is crucial for cellular energy production and tumour suppression, acting as a component of mitochondrial complex II. GABPA is a nuclear ETS transcription factor known to bind and activate mitochondrial genes required for electron transport and oxidative phosphorylation, often forming a heterodimer with GABPB1.

Some other examples include Recurrent non-coding variants in the CD20 promoter that abolish an ETS motif. This loss leads to down regulation of CDC20, establishing a transcriptional program promoting metastatic progression. CTCF binding site disruption: somatic mutation e.g. Chr 5: 111.887.319 G>A can occur within a CTCF insulator motif. These mutations disrupt the binding of the CTCF protein, essential for maintaining chromatin loops. This leads to dysregulation of APC, a tumour suppressor. Another example is *DPH3/NDUFB9*. Recurrent mutations in the promoter of these genes have also been shown to ablate predicted ETS or Sp1 binding motifs. Unlike TERT, which gains a binding site, these mutations function by destroying the existing regulatory architecture.

6. Kinase Fusions- An Example of Genomic Rearrangements

Genomic rearrangements resulting in activating kinase fusions have been increasingly described in several cancers including melanoma. Turner et al examined genomic rearrangements in melanoma identifying involvement of *BRAF, RET* and *ROS1* genes in different subtypes of melanoma but all tumours with genomic rearrangements lacked the common driver mutations [31]. These kinase fusions were found in only 3% of melanomas examined but in 9% of melanomas lacking hotspot mutations in common driver genes. Though uncommon in cutaneous melanoma, gene fusions may have therapeutic implications [31].

Spitzoid neoplasms are a group of melanocytic tumours with distinctive histopathological features. They include benign spitz naevi, malignant Spitzoid melanoma and a group of intermediate lesions with borderline histopathological features and uncertain biological behaviour, atypical Spitz tumours. Alterations in common melanoma-associated oncogenes are typically absent. Weisner et al showed that these neoplasms harbor kinase fusions of *ROS1* (17%), *NTTRK1* (16%), *ALK* (10%) and *RET* (3%) in a mutually exclusive pattern. They stimulate oncogenic pathways and are found in all members of this group of neoplasms, including Spitz naevi (55%), atypical Spitz tumours (56%) and spitzoid melanoma (39%). Metastatic spitzoid melanoma maybe a target for kinase inhibitors [32].

The occurrence of kinase fusions in the entire spectrum of spitzoid neoplasms suggests that these events occur early in the pathogenesis of these neoplasms, Therefore, the fusions are necessary but not sufficient for malignant transformation, analogous to mutations in oncogenes found in melanocytic neoplasms. Unfortunately, these fusions are unlikely to be helpful in separating benign from malignant neoplasms.

The TCGA database identified fusions in *BRAF* and *RAF1* but not *ALK, ROS1, RET* or *NTRK1* in their set of 328 cutaneous melanomas. Since then, *ALK* fusions were reported in 13% of acral lentiginous melanoma but none identified in mucosal melanoma [33]. These studies suggest that the genes involved in oncogenic fusion events in melanoma maybe subtype specific. Turner et al screened for kinase rearrangements in different subtypes of melanoma in tumours from 59 patients. They identified genomic rearrangements in tumours from 4 patients involving *BRAF, RET* and *ROS1*. These occurred in superficial spreading,

acral lentiginous and unknown primary subtypes. One was found to be an *ARMC10-BRAF* fusion that had not been previously reported in melanoma [31].

Oncogenic *ALK* fusions occur in several types of cancer and more recently Couts et al examined *ALK* fusions and response to ALK inhibitors in melanoma. Melanomas expressing *EML4-ALK* were sensitive to ALK inhibitors, but they also identified several isoforms of *ALK* and rarer fusion variants that were not [34].

Fusions occur in different subtypes of melanoma, but all these tumour subtypes lack known driver mutations. They may be more common than previously thought and should be explored in melanomas lacking known driver mutations.

7. Discussion

The melanoma landscape has become clearer over the last decade. Training in and the use of dermatoscopy, teaching algorithms and clinico-histological correlation have helped in the separation and identification of a normal naevus from one that is defined as atypical. Classification by histology and immunostaining separates the diagnosis of melanoma in situ (MIS) and early invasive melanoma. The resulting picture is one of a rising 45° line in the diagnosis of MIS and a relatively flat horizontal line for death from melanoma. There are clear management guidelines for these levels of malignancy but for the clinician there remains a grey area between the normal and the atypical naevus and particularly the histological grading of mild, moderate and severely atypical naevus which has been shown to arbitrary and poorly reproducible.

How many MIS defined lesions would progress to invasive melanoma, this is still unclear, I would suggest 50% or less. The guidelines suggest excision with a 5 mm margin. There is no clear evidence to support this, but it remains excepted clinical practice, and we pat ourselves on the back and say all is clear but is this really the case?

A wider excision has done little harm, and we have possibly identified a subset of patients who benefit from closer monitoring. Of more relevance is the 10 mm wider excision for invasive melanoma which may become a cause of morbidly particularly on the head and neck. Usually, but not always confined to the older melanoma sufferer.

Morphology and histology are now no longer enough to properly define melanoma subsets. Molecular and genetic studies may yet redefine the classification of these subsets and give a clearer view of levels of malignancy in melanoma. Of probably more consequence is the identification of the full spectrum of genetic alterations driving melanoma is fundamental to understanding the molecular aetiology of melanoma and progressing towards more advanced, targeted therapies.

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