ROLE OF PROMOTER AND SPLICING VARIATIONS IN SHELTERIN COMPLEX GENES IN MELANOMA DEVELOPMENT AND PROGRESSION

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Discoveries in cell signaling mechanisms have provided better understanding of melanoma progression. Deleterious mutations, structural alterations or epigenetic events have been reported but the functional role of variations in non-coding regions, such as those in TFs binding sites, or in splicing regions, with generation of transcript isoforms and alternative splicing events, is still to be elucidated. By studying metastatic melanoma cells lines and paired primary and metastatic melanomas, together with germline DNA, we aimed to link somatic and germline changes, with a focus on promoter and splicing variants. The MAPK pathway may be compromised at distinct stages, with the BRAFV600E already found in benign nevi, representing an early event. The sequential order of genetic events in late-stages, including those in TERT promoter and CDKN2A/p16, both involved also in melanoma predisposition, is not clarified. In our cohort the activation of BRAF was identified in most cases, as CDKN2A/p16 LOH, and co-occurred with TERT promoter variants suggesting a link between MAPK activation that activates ETS1-TF by ERK, and altered TERT promoter bearing ETS-binding sites. Novel TERT promoter variants are being functionally characterized. As we showed for germline variants in UTRs of CDKN2A, having an effect on the translation potential, TERT promoter variants seem to underlie susceptibility but also contribute to late stage melanomagenesis. Little is known about the role in melanoma progression of another shelterin complex gene, POT1, and particularly of alternative splicing variants, although exon skipping in some transcripts, giving rise to splice variants is recognized as for CDKN2A/p14ARF. Hence we functionally and quantitatively characterized two novel splicing germline variants in constitutional RNA and metastatic melanoma cell lines. Our data unveil that variations in non-coding regions and alternative splicing play a role in both melanoma susceptibility and progression.