In-depth Molecular and Immune Characterization of Melanomas with Heterogeneous PTEN Expression

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Background

- Previous studies have shown that loss of expression of the PTEN tumor suppressor in melanoma metastases is associated with:
  - Increased expression of phosphorylated (activated) AKT (P-AKT), consistent with increased activation of the PI3K-AKT signaling pathway. [1]
  - Shorter overall survival (OS) and increased risk of brain metastasis in stage IIIIB/C melanoma patients.[1]
  - Resistance to FDA-approved targeted therapies. [2,3]
  - Decreased T-cell infiltration and resistance to anti-PD-1 immunotherapy.[4]

- While the overwhelming majority of melanoma metastases demonstrate uniform patterns of PTEN expression, we have identified a rare (~3%) subset of melanomas with distinct regions of (+) and (-) PTEN protein expression by IHC.

- In depth molecular and immune analyses were performed on PTEN (+) and (-) regions of melanoma metastases with heterogeneous expression to improve our understanding of the effects of PTEN loss in this disease.

Material and Methods

- Expression of proteins involved in cancer signaling pathways (n=42) and immune populations/ regulators (n=40) was quantified separately in PTEN (+) and (-) regions on FFPE slides by in situ NanoString® Digital Spatial Profiling (DSP) [Fig. 1].

- DNA
  - Somatic mutations and CNVs by 200-gene NGS panel
  - DNA methylation by Illumina Infinium Human Methylation 450.

- RNA
  - Gene expression by NanoString® PanCancer Pathway and Immune Profiling panels

Analysis included 8 metastases with PTEN (+) and (-) regions from 7 metastatic melanoma patients

- Metastatic sites: Lymph nodes (n=4), Lung (n=3), Parotid (n=1)

Results

- Volcano plots for genes in cancer immune (Upper) and cancer signaling pathway (Lower) panels. PTEN (-) regions demonstrated significantly ↓ expression of PTEN, CCNA1 and ISG15, and ↑ expression of MAPK10 and MAGEA12, compared to PTEN (+).

Conclusions

- Focal loss of PTEN expression appears to be driven primarily by genetic events in the PTEN gene, not by changes in DNA methylation.

- Loss of PTEN correlated with significant differences in both molecular and immune features.

- The findings add to our understanding of the associations and consequences of PTEN loss in melanoma, and highlight the potential for significant molecular and immunological in intratumor heterogeneity in this disease.

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References

5. AACR Annual Meeting 2017, #3955.