Splicing regulatory kinase UHMK1 is associated with immune remodeling and T-cell exhaustion in melanoma

Gabriela Ferreira Dias1 , Isabela David Cardoso1 , Enzo Marques Panepucci1 , Lisa Latzko2 , Vanessa Cristina Arfelli2 , Tathiane Maistro Malta1 , Sebastian Vosberg2 , Philipp A Greif2 , Leticia Fröhlich Archangelo1 1University of São Paulo (USP), Ribeirão Preto Medical School (FMRP-USP), Ribeirão Preto, Brazil, 2LMU Klinikum, Munich, Germany

Background: Splicing alterations can reshape cancer cell transcripts and affect tumor immunogenicity via splicing-derived neoantigens. UHMK1, a splicing regulatory kinase overexpressed in melanoma, particularly in metastasis, is related to malignant phenotypes (unpublished data). Here, we investigated whether UHMK1 expression is associated with immunerelated programs in melanoma. Method: Nanopore long-read RNA-seq was analyzed in A375 and WM793 melanoma cells with UHMK1 knockout or overexpression. TCGA-SKCM samples (Bulk RNAseq) were stratified by UHMK1 expression (Q3/Q1), followed by differential expression (DESeq2) and GSEA. CIBERSORTx estimated tumor composition using a melanoma scRNA-seq reference (GSE115978). In the same dataset, differential expression (MAST), and pathway activity (Ucell) were evaluated across tumor microenvironment (TME) populations. Results: UHMK1 knockout increased antigen presentation and pro-inflammatory signaling, including JAK/STAT activation, while overexpression showed the opposite trend. In TCGA-SKCM, UHMK1-High tumors showed reduced global immuneresponse programs in both primary and metastatic melanoma, although UHMK1-High metastatic tumors exhibited increased antigen-presentation genes (TAP1, B2M, CD274) and IFN-α/IFN-γ enrichment. CIBERSORTx revealed a strong association between UHMK1 and tumor composition in primary melanoma (R^2=0.226, p=0.001), mainly involving malignant, monocyte/macrophage, and CD8 T-cell populations. This association was weaker in metastases (R^2=0.024, p=0.001) and driven mainly by CD8 T cells, with UHMK1-Low tumors showing more CD8 and fewer exhausted CD8 cells. Single-cell analysis detected UHMK1 across all TME cell types at different proportions, with higher expression in exhausted than non-exhausted CD8 T cells. In exhausted CD8 T cells, UHMK1 was associated with protein translation and suppressive programs, while UHMK1-expressing CD4 T cells showed activated, metabolically reprogrammed and antitumor-associated programs. Several overexpressed genes were also upregulated in UHMK1-High TCGA tumors. Conclusion: Overall, UHMK1 expression is associated with immune regulation in melanoma, supporting a link between splicing regulation and tumor immunogenicity, providing a basis for investigating its potential impact on immunotherapy response in melanoma.