746 **POST-TRANSCRIPTIONAL MODULATION OF TAPASIN: NOVEL MECHANISMS DRIVING IMMUNE ESCAPE, METASTASIS AND TUMOR-IMMUNE CELL CROSSTALK IN MELANOMA**

[1]Yuan Wang*, [2]Chiara Massa, [3]Anja Mueller, [4]Theresa Kordaß, [1]Christoforos K Vaxevanis, [5]Stefan Eichmüller, [1,2]Barbara Seliger. *[1]Institute for Pathology, Section Immunopathology, Martin Luther University of Halle-Wittenberg, Halle, Sachsen-Anhalt, Germany; [2]Institute of Translational Immunology, Medical School 'Theodor Fontane' and Faculty of Health Sciences, Brandenburg an der Havel, Land Brandenburg, Germany; [3]Institute for Medical Immunology, Halle, Sachsen-Anhalt, Germany; [4]Universitätsmedizin Greifswald, Greifswald, Mecklenburg-Vorpommern, Germany; [5]Research Group GMP and T Cell Therapy, German Cancer Research Center (DKFZ), Heidelberg, Baden-Württemberg, Germany*

Background Impaired expression of key components of the HLA class I antigen-processing and presentation machinery (APM) enables tumor cells to evade $CD8^+$ T cell-mediated recognition and elimination. Emerging evidence implicates post-transcriptional regulation via RNA-binding proteins (RBPs) and microRNAs (miRNAs) as a critical mechanism underlying this downregulation. Although tapasin is essential for optimal HLA-I peptide loading, the specific miRNAs and RBPs that target tapasin, their effects on melanoma immune escape and their contributions to tumor microenvironment (TME) remodeling remain poorly defined. Here, we explore the role of the posttranscriptional control and its functional consequences in melanoma progression, TME composition and immune modulation.

Methods MiRNAs and RBPs binding to the tapasin 3′ untranslated region (3′UTR) were identified using biotinylated RNA pulldown, RNA sequencing and mass spectrometry. Direct interactions of selected miRNA (miR-155) and RBP (hnRNP C) were confirmed by luciferase reporter assays and CRISPR/Cas9-mediated deletion of the candidate binding sequence. Functional effects on HLA-I surface expression were assessed by flow cytometry. $CD8^+$ T cell recognition and NK cell cytotoxicity were measured in co-culture assays. Expression correlations and the prognostic impact were analyzed in TCGA-SKCM and independent in silico cohorts. Finally, the role of hnRNP C in affecting the phenotype of tumor-associated macrophages (TAMs), on melanoma metastasis using transwell migration assays, cytokine profiling and single-cell seq dataset analysis.

Results miR-155-5p directly engages a repressive element within the 3′UTR of tapasin and its CRISPR/Cas9-mediated excision abolishes its regulatory activity. MiR-155-5p overexpression elevates tapasin levels, augments HLA-I surface presentation, and enhances $CD8^+$ T cell recognition, but a reduced NK cell cytotoxicity. In contrast, hnRNP C binds to the tapasin 3′UTR to inhibit its translation resulting in diminished HLA-I expression on melanoma cells. Analyses of TCGA-SKCM and independent cohorts reveal that high miR-155-5p and low hnRNP C expression associate with increased tapasin abundance and improved overall patients' survival. Finally, in the TME, hnRNP C synergizes with factors secreted by TAMs to promote melanoma cell migration and metastatic dissemination, in part via a CXCR3-hnRNP C-MIF signaling axis.

Conclusions This study identifies miR-155-5p and hnRNP C as key post-transcriptional regulators of tapasin, with opposing effects on the HLA-I antigen-presentation pathway and demonstrable clinical relevance in melanoma. Furthermore, we reveal novel, noncanonical functions of miR-155-5p and delineate how hnRNP C influences tumor-associated macrophage-driven metastatic behavior. Taken together, our data nominate both miR-155-5p and hnRNP C as promising biomarkers and potential targets for melanoma immunotherapy.

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