21

EXPLORING THE EFFECT OF SAMHD1 ON TUMOR SUPPRESSION IN CUTANEOUS MELANOMA

Silvia Angori[1], Sofi Vikström[1,2], Alessandra Muni[1], Nikolas Herold[3], Andreas Lundqvist[1], Stina Wickström[1,] Georgios Rassidakis[1,2], Hanna Eriksson[1,4 *]

[1] *Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden*

[2] *Department of Clinical Pathology and Cancer Diagnostics, Karolinska University Hospital, Stockholm, Sweden*

[3] *Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden*

[4] *Theme Cancer, Skin Cancer Center, Karolinska University Hospital, Stockholm, Sweden*

Corresponding Author: Hanna Eriksson hanna.eriksson.4@ki.se

Background: Cutaneous melanoma (CM) is one of the most aggressive of all skin cancers and has the highest mortality. Although treatments with immune checkpoint inhibitors (ICIs) have improved the survival rate of CM patients, approximately 50% of these patients still die from the disease. SAMHD1, a key regulator of innate immune responses and DNA damage repair, can act as a tumor suppressor in various malignancies. We hypothesize that SAMHD1 expression confers a survival advantage by enhancing the anti-tumor immune response in CM. We propose that the loss of SAMHD1 in mCM promotes tumor progression through dual mechanisms: first, bydysregulating dNTP pools, leading to replication stress and cell cycle disruptions, and second,by hyperactivating the STING pathway, which enhances the expression of immune-suppressivemolecules like PD-L1, thereby limiting immune cell infiltration and contributing to immune evasion. This project aims to investigate the impact of SAMHD1 in inhibiting the STING- TBK1 axis in CM, which may result in improved response to immunotherapy in melanoma.

Methods: To evaluate the impact of SAMHD1 status, we have generated commercially available and patient-derived SAMHD1 knock-out (KO) cells by CRISPR/Cas9 technology. Tumor- infiltrating lymphocytes (TILs) from melanoma patients and NK cells from healthy donors were co-cultured with SAMHD1-wt and -KO melanoma cells to evaluate how the presence ofSAMHD1 can influence the immune response.

Results: Our data showed that higher SAMHD1 expression is significantly associated with better overall survival (458 CM patients, TCGA data) with a proportion of high-expressers as long-term survivors after adjustment for lymphocyte infiltration. This result supports the hypothesis thatthe expression of SAMHD1 has a positive effect on survival in CM. Next, we have corroborated the association between loss of SAMHD1 and STING pathway activation in melanoma cell lines. Indeed, cells lacking SAMHD1

showed hyper-activation of the STING pathway by increased expression of downstream target genes such as ISG15, IFI16, and CXCL10.

Conclusions: By exploring the role of SAMHD1 in CM and examining its modulation of the immune landscape, we aim to lay the groundwork for novel therapeutic strategies that could improve outcomes for CM patients.