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EXPRESSION OF SAMHD1 IN BRAIN METASTASISED CUTANEOUS MELANOMA

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Background: Cutaneous melanoma (CM) has the highest mortality rate among all skin cancers. It is a leading cause of brain metastases, alongside lung and breast cancer, with 40-50% of patients with metastatic CM developing melanoma brain metastases (MBM). Historically, MBM had a median overall survival (OS) of less than six months, but advancements in therapies have extended OS. However, morbidity and mortality remain high, with current treatments offering a median survival of 5-9 months. Sterile alpha motif and Histidine Aspartate Domain-containing protein 1 (SAMHD1), a key regulator of the innate immune system and DNA repair mechanisms, have demonstrated the ability to suppress aggressive tumour behaviours in various cancers. When SAMHD1 is lost, there is an enhanced activation of the STING-TBK1 pathway, a mediator of inflammation that facilitates tumour growth, leading to an immunosuppressive microenvironment. This study aims to explore the expression of SAMHD1 in clinical melanoma samples.

Materials and Methods: The study included one retrospective clinical cohort from Karolinska University Hospital comprising brain metastases with paired primary CM and metastases (n=190) and tissue microarrays (TMA) melanoma samples from Zurich (n=228). Samples were stained with hematoxylin and eosin and a double immunohistochemical staining for SAMHD1/CD68 to distinguish CD68+ macrophages from melanoma cells and serve as an internal control for staining intensity. Tumour cells were assessed for SAMHD1 intensity and categorised into high SAMHD1 (intensity 2, i.e.,

same intensity as a macrophage) and low SAMHD1 (0-1, i.e., no staining and weak staining). Expression of SAMHD1 was also categorized (0=0%, 1=<25%, 2=25-75%, 3=>75%).

Results: The retrospective clinical cohort comprised 90 brain metastases with paired primary CM (n=36) and metastases (n=64). The Zurich TMA cohort consisted of samples from brain metastases (n=96), primary tumours (n=42), and metastases from other sites (N=90). A significant loss of SAMHD1 intensity (low SAMHD1) was observed in both cohorts. In the retrospective clinical cohort, 94% of samples demonstrated low SAMHD1 intensity, most notably in metastases (98%). Similarly, the Zurich TMA cohort showed a high degree of low SAMHD1 samples (83%), with the greatest number of Low SAMHD1 in metastases (91%). A higher degree of SAMHD1 expression was observed in the SAMHD1 high group compared to the low SAMHD1 group in both cohorts.

Conclusions: These findings suggest that SAMHD1 may play a role in CM, warranting further investigation into its potential correlation with other immune markers.