OS12.7.A CHARACTERIZATION OF INTRA-TUMORAL HETEROGENEITY AND DIFFERENTIAL IMMUNE ACTIVATION DURING MALIGNANT PROGRESSION OF MENINGIOMAS ON SINGLE CELL LEVEL

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BACKGROUND: As the most common intracranial tumor, meningiomas have caused increasing interest in the field of medical research. Based on their mutational profile, meningiomas can be separated into two main groups: NF2 altered meningiomas, which can occur at WHO grades 1 to 3, and non-NF2 mutant meningiomas with mutations in other genes, such as TRAF7, AKT1, KLF4, and SMO, which are usually of WHO grade 1. While this means that non-NF2 mutant meningiomas usually follow a benign course, risk stratification for NF2 mutant meningiomas remains difficult. As of now, the underlying mechanisms contributing to the malignant phenotype of some NF2 mutant

meningiomas remained unknown, even though some molecular markers have been associated with an increased risk of recurrence. Here, we sought to characterize robust molecular subgroups for meningiomas and identify the critical steps in malignant progression of these tumors. MATERIAL AND METHODS: We applied bulk RNA sequencing and proteomic analyses for 44 meningioma samples as well as single nuclei RNA sequencing analyses for an additional set of 26 meningiomas with a total of 46,002 nuclei. Both datasets comprised samples across the molecular landscape of meningiomas and WHO grades 1, 2, and 3. RESULTS: The meningioma subgroups previously identified on epigenomic level were found consistently also on transcriptomic, proteomic, and phospho-proteomic levels. In addition, strong differences in numbers and types of infiltrating immune cells between subgroups became apparent. A decreased number of infiltrating macrophages and an activation to a more proinflammatory phenotype was observed for WHO grade 3 tumors. This observation correlated with lower expression levels of *CSF1* in tumor cells of WHO grade 3 meningiomas, which was predicted to stimulate macrophages in WHO grade 1 and 2 tumors. Moreover, we identified several tumor cell subpopulations, each defined by a distinct phenotype, shared across samples. Their proportions in the tumor strongly depended on tumor grade. Especially a subpopulation characterized by an elevated stress response and TGFβ signaling activity was found specifically in WHO grade 3 cases. CONCLUSION: Our findings establish molecular subgroups for meningiomas that are robust across multiple levels with characteristic differences in pathway activities and demonstrate a subtype-specific immune activation, both of which may be basis for novel treatment strategies.