EP-04. ACTIVATION OF THE IL6/STAT3 PATHWAY IN CHILDHOOD EPENDYMOMA IS ASSOCIATED WITH A PRO-INFLAMMATORY TUMOR MICROENVIRONMENT AND A POOR PROGNOSIS
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To aid development of immunotherapy for poor outcome Group A ependymoma (EPN) in children we sought to identify the molecular pathway underlying the adverse pro-inflammatory phenotype associated with this molecular subgroup. We previously showed the importance of immunological factors and that an anti-tumor immunophenotype was critical in survival whereas a pro-inflammatory phenotype was associated with a poor outcome. We contrasted gene expression profiles of patient tumor samples from Group A EPN to the more clinically favorable Group B, identifying potential molecular pathways associated with the Group A immunophenotype. Strikingly, we found a robust expression signature implicating the IL6/STAT3 pathway in Group A tumors. Comparison of transcriptomic profiles of Group A and Group B demonstrated significant overexpression both IL6 and STAT3 in Group A. High overexpression of STAT3 driven IL8 and SOCS3 was also seen in Group A. Western blot analysis of tumor samples from Groups A and B showed a significantly elevated ratio of pSTAT3:STAT3 in Group A, denoting activation of STAT3. Measurement of IL6 secretion from primary ex-vivo tumor cells showed a significantly higher secretion by Group A than Group B. To further investigate the role of the IL6/STAT3 pathway, we utilized a novel EPN cell line (811) with the transcriptome characteristics of Group A. Similar to Group A tumors, 811 secretes high levels of IL-6 and has elevated STAT3 activation. Loss of STAT3 resulted in reduction of downstream targets and apoptosis. The elevated IL6 from 811 induced a contact-independent polarization of myeloid cells to a pro-inflammatory phenotype. CD14+ cells treated with 811 conditioned media showed a significant increase in IL8 secretion. The IL6/STAT3 pathway is active in Group A EPN and is important in maintaining tumor growth in a pro-inflammatory microenvironment. Effective Group A-targeted immunotherapy for children with EPN may require alleviation of this potentially immunosuppressive pathway.