O6.09. PROSTAGLANDIN E RECEPTOR-4 ACTIVATION REGULATES TRYPTOPHAN METABOLISM IN HUMAN MALIGNANT GLIOMAS
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Malignant gliomas generate a local immunosuppressive microenvironment as well as systemic immunosuppression. Tryptophan-2,3-dioxygenase (TDO)-mediated tryptophan metabolism and the production of immunosuppressive prostaglandins relevantly contribute to this inhibition of anti-glioma immune responses. We now connect these two critical immunosuppressive pathways by demonstrating that prostaglandins enhance TDO expression and enzymatic activity in malignant gliomas via activation of prostaglandin E receptor-4 (EP4). Stimulation with prostaglandin E2 (PGE2) concentration-dependently upregulates TDO-mediated kynurenine release in human glioma cell lines, while knockdown of the PGE2 receptor EP4 inhibits TDO expression and activity. In tissue of human malignant gliomas expression of the PGE2-producing enzyme cyclooxygenase-2 (COX-2) and its receptor EP4 are associated with TDO expression both on transcript and protein level. Of clinical relevance, high expression of EP4 correlates with poor survival in patients with gliomas of the WHO grades III and IV. Importantly, treatment of glioma cells with an EP4 inhibitor decreased TDO expression and activity. In summary targeting EP4 may inhibit both immunosuppressive COX-2 signaling as well as tryptophan degradation and thus could provide a novel immunotherapeutic avenue for the treatment of malignant gliomas.