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# Proteome and phosphoproteome analysis identifies STAT1 as a novel target in different grade meningiomas

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## Abstract

Meningiomas are slow growing tumours of the meninges that affect brain and spinal cord. They account for a quarter of all primary brain tumours of the central nervous system. Accordingly to the WHO classification system, meningiomas are classified as grade I, atypical grade II and malignant grade III. Symptoms include headaches, focal neurological signs depending on localisation and seizures. The standard of treatment for these tumours is (radio)surgery. Nevertheless, it is estimated that one third of meningiomas cannot be operated or can be only partially resected, often leaving patients with significant morbidity. Current chemotherapies are not effective therefore it is a great medical need to find novel therapeutic options. We aimed to identify novel targets/biomarkers by analysing proteome and phosphoproteome of different grade meningiomas. Frozen tumour specimens as well as meningioma-derived primary tumour cells were analysed by mass spectrometry to decipher proteome and phosphoproteome. -Phosphoproteins were isolated by an additional purification step. Overall we analysed 22 meningiomas (8 grade I, 8 grade II and 6 grade III) for the proteome and 14 for the phosphoproteome (5 grade I, 5 grade II and 4 grade III). Comparative studies were performed to identify aberrantly overexpressed proteins and dysregulated pathways compared to healthy human meninges (N=3). Among the proteins found significantly upregulated in meningioma

vs. normal controls we identified STAT1, a member of the Jak/STAT signalling pathway. Validation studies performed on primary meningioma cells confirmed that the total amount of the protein was overexpressed about four times compared to normal human meningeal cells. Additionally, both phosphorylation sites (Y701 and S727) on STAT1 were aberrantly activated in meningioma cells but not in meningeal cells. Immunohistochemical analysis confirmed an upregulation of phosphorylated STAT1(Y701) especially on grade III meningiomas, in agreement with expression studies, although with high variability across samples. When the Jak/STAT signaling pathway gets activated in response to cytokines and growth factors, STAT1 is phosphorylated by activated JAKs and translocate into the nucleus to regulate gene expression. In primary meningioma cells we found that the amount of cytoplasmic pSTAT1(Y701) was markedly increased in vitro, without interferon stimulation and also in serum-free conditions, suggesting a cytokine-independent mechanism for pSTAT1 activation. Finally, STAT1 knocked down resulted in a significant reduction of cellular proliferation showed as a decrease in Ki67-positive cells and a decrease expression of Cyclin D1. These data altogether suggest STAT1 as a novel potential target in meningiomas.