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Expression of Growth Differentiation Factor-15 (GDF-15) in human gliomas and its functions in glioblastoma cell lines

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GDF-15, a distant member of the TGF-β superfamily, was shown to be a p53 target gene and is considered to exert anti-tumorigenic and pro-apoptotic functions. The aim of the present work was to investigate the expression of GDF-15 in diffusely infiltrating astrocytomas of different malignancy grades. Putative functions of GDF-15 were analysed using human glioma cell lines. A mutational analysis of GDF-15 expressed by glioblastomas and glioma cell lines was also undertaken, as well as attempts to elucidate aspects of GDF-15 signalling.

The GDF-15 mRNA expression level was found to be similar in secondary glioblastomas (WHO IV) and their precursor tumours, the diffuse astrocytomas (WHO II) and anaplastic astrocytomas (WHO III). This expression pattern points to a role of GDF-15 in the initial stages of tumour development, rather than in tumour progression. We found a significant difference in GDF-15 expression level between primary and secondary glioblastomas, tumours which are known to arise through different genetic pathways. We could visualize GDF-15 by immunohistochemistry in one primary glioblastoma sample. Interestingly, GDF-15 protein was only localized in certain regions of the tumour, probably reflecting the histopathological heterogeneity, a typical feature of glioblastomas. GDF-15 cDNA 5 primary glioblastomas and 3 glioma cell lines was cloned and sequenced, but no mutations could be found.

The GDF-15 expression level in human glioma cell lines was not correlated to the p53 status (wild-type, mutated or null), which suggests that endogenous p53 does not necessarily induce increased expression of GDF-15 in these cell lines. Even though the GDF-15 expression level did not correlate to the basal proliferation rate either, we were able to show that the endogenous GDF-15 plays a role in modulating proliferation in most of the cell lines analyzed. Indeed, by applying neutralizing antibodies against GDF-15, we observed an attenuation of the mitogenic activity in 9 of the 10 cell lines tested. Blocking of endogenous GDF-15 also decreased invasiveness of two cell lines and increased invasiveness of one of

them. However, recombinant GDF-15 did not significantly influence invasiveness in any of the cell lines and increased proliferation only slightly in 5 of them. These results suggest that GDF-15 has a pro- rather than anti-tumorigenic effect on the glioma cell lines analyzed. In general, the effects of GDF-15 seem to vary significantly among the different cell lines. Neither recombinant GDF-15 nor the blocking serum had any effect on the spontaneous apoptotic rate of glioma cells.

We showed further that recombinant GDF-15 induces phosphorylation of ERK and Akt in one of the cell lines under study. However, since these cells were the least affected by recombinant GDF-15 as well as by the blocking antibodies, we assume that GDF-15 may also have other functions than the modulation of proliferation and invasiveness. Finally, we showed that, unlike suggested by some authors, GDF-15 does not signal through binding to the TGF-β receptor.

In conclusion, the present work allows new insights into the expression of GDF-15 in human gliomas of different malignancy grades, into the function of GDF-15 in glioma cell lines and into the GDF-15 signalling pathway. These results might even help to consolidate our knowledge about the role of GDF-15 in human malignant tumours.