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GLIAL EXPRESSION OF NEUTRAL ENDOPEPTIDASE-24.11 (NEP) IN TUMORS ARISING FROM NEUROTRANSPLANTATION OF RAT FETAL CORTEX CORRELATES WITH EXPRESSION OF TRANSFORMING GROWTH FACTOR-ALPHA

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Authors

BACK, SA
COLON, M
WANG, W
et al.

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GLIAL EXPRESSION OF NEUTRAL ENDOPEPTIDASE-24.11 (NEP) IN TUMORS ARISING FROM NEUROTRANSPLANTATION OF RAT FETAL CORTEX CORRELATES WITH EXPRESSION OF TRANSFORMING GROWTH FACTOR-ALPHA. S.A. Back*, M. Colon*, W. Wang*, J.H. Fallon*, F.L. Meyskens, Jr.** and S. Loughlin*. Depts. of Pediatrics, Anatomy and Neurobiology and the Clinical Cancer Center, University of California, Irvine.

The enzyme NEP is identical to the common acute lymphocytic leukemia antigen (CALLA). It is a tumor marker associated with improved prognosis in children who have acute lymphocytic leukemia, and is also expressed in high amounts in some human glioma cell lines. We report here a unique model to study NEP expression in experimentally-induced tumors arising after neurotransplantation. A fluorescent histochemical method (Back and Gorenstein, J. Comp. Neurol. 296:130-158) was used to localize NEP in brain sections from fetal rat (embryonic day (ED) 14-16) or adult rats which survived 4-16 weeks after transplantation of a suspension of rat fetal cortical cells (ED 14-16) into the caudate putamen. Tissue morphology was assessed by Nissl stain or ethidium bromide fluorescent counterstain. Glia were visualized by immunocytochemical localization of the glial marker, glial fibrillary acidic protein (GFAP) or transforming growth factor-alpha (TGFα). The transplant site typically contained a mass which compressed the surrounding caudate. The apparent tumor contained cell types of varying size and morphology. A fluorescent double-labeling technique demonstrated several types of glia containing both NEP and GFAP: a) many reactive astrocytes circumscribing the tumor; b) scattered protosplasmic and gemistocytic-like astrocytes within the tumor; and c) occasional nests of cells which stained for NEP and were surrounded by numerous astrocytic processes. Within the tumor, glial staining for both TGFα and NEP was often observed along the injection site. Occasional "satellite" clusters of cells, distinct from the main tumor, contained many TGFα-positive glia surrounded by rich NEP staining. An examination of NEP staining in fetal rats (ED14-16) indicated that there was extensive staining in the CNS which paralleled that which we have previously described in the adult. Relatively low levels of GFAP staining were observed in the fetal brain. The cortical mantle used in the transplants displayed very little GFAP staining. In the fetal rat brain, as in the adult brain, we found NEP expression to be largely unassociated with glial cells. However, in our surviving fetal cortical transplants, coexpression of NEP and glial elements is induced. The cause of tumor formation following the transplants is unclear. It may be significant that the center of the tumor contained many TGFα-positive glia which might supply this growth factor to sustain the growth of the mass. Many of these glia also contained NEP. Given that TGFα was shown to be selectively associated with malignant gliomas in one series of 20 patients, the coexpression of two tumor markers within these glia may be indicative of the proliferative potential of the transplants. This transplant model may be useful to study the role of NEP in the growth of malignant gliomas and should be useful to test the potential therapeutic role for NEP inhibitors in slowing the growth of malignant gliomas in children. S.A.B. is a Giannini Foundation fellow.