

Letter to the Editor

Nerve Growth Factor and Neuroblastoma

Garin-Chesa et al. found that monoclonal antibody to human NGF receptor (NGF-R MAb) failed to stain any of eight neuroblastomas (4). These findings are predictable from our earlier work but do not fit in with more recent literature (9,11,17,18,20,21,23,24).

NGF is a polypeptide which has profound effects on sensory and sympathetic ganglia (10,14). Neuroblastoma is a malignant tumor of the sympathetic nervous system. It has been estimated that 39 out of every 40 neuroblastomas arising in early infancy regress spontaneously (1). It is quite common to see a collection of ganglion cells in a neuroblastoma, and occasionally a child dying from a metastatic neuroblastoma is found to have primary tumor which has completely matured into a ganglioneuroma (a benign tumor) (12). It is conceivable that in such cases maturation is following the growth of the tumor, but it only rarely proceeds fast enough to catch up with the spread of the disease.

More than 15 years ago we concluded that NGF probably has no role in the treatment of neuroblastoma (9,24). This statement was based on the following evidence. Sera from 621 normal individuals and from 28 children with neuroblastoma contained similar levels of NGF. A polyclonal antiserum raised in rabbits against mouse NGF neither stained neuroblastoma nor did it (or mouse NGF) have any effect on primary cultures of human neuroblastoma. Injection of NGF into three children with neuroblastoma failed to influence the course of the tumor. Although we had not realized it at the time, it is possible that our negative results might have been owing to non-reactivity of mouse NGF with human NGF-R. Indeed, monoclonal antibodies raised by Ross et al. (19) to human NGF-R have been found to be human specific and do not recognize rat or chick NGF-R.

Overwhelming evidence accumulated in the last decade suggests that NGF ought to be important in patients with neuroblastomas. NGF induces morphological and biochemical changes in human neuroblastoma cell lines, and NGF receptor (NGF-R) has been found in cultured human neuroblastoma cells (6-8,11,17,18,20-23). Neuroblastomas have been reported to be associated with certain abnormalities of chromosome 17, and perhaps it is not a coincidence that the NGF-R gene resides on this chromosome (17q 21-qter) (3,5,8). It is possible that a greater understanding of the interaction of factors such as insulin and IGF-II, which not only mimic the action of NGF but can affect the binding of NGF to neuroblastoma cells (2,13,15,16), will help to ascertain the regulatory role of these molecules in health and disease.

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Literature Cited

1. Beckwith JB, Perrin EV: In situ neuroblastomas: a contribution to the natural history of neural crest tumors. *Am J Pathol* 43:1089, 1963
2. Berthold F: Current concepts on the biology of the neuroblastoma. *Blut* 50:65, 1985
3. Biedler JL, Ross RA, Shanske S, Spengler BA: Human neuroblastoma

cytogenetics: search for homogeneously staining regions and double minute chromosomes. In Evans AE, ed. *Advances in neuroblastoma research*. New York, Raven Press, 1980, 81

4. Garin-Chesa PG, Rettig WJ, Thomson TM, Old LJ, Melamed MR: Immunohistochemical analysis of nerve growth factor receptor expression in normal and malignant human tissues. *J Histochem Cytochem* 36:383, 1988
5. Gilber F, Feder M, Blaban G, Brangman D, Lurie DK, Podolsky R, Rinaldt V, Vinikoor N, Weisband J: Human neuroblastomas and abnormalities of chromosomes 1 and 17. *Cancer Res* 44:5444, 1984
6. Haskell BE, Stach RW, Werrbac-Perez K, Perez-Polo JR: Effect of retinoic acid on nerve growth factor receptors. *Cell Tissue Res* 247:67, 1987
7. Jensen LM: Phenotypic differentiation of aphidicolin-selected human neuroblastoma cultures after long-term exposure to nerve growth factor. *Dev Biol* 120:56, 1987
8. Klinz FJ, Yu VC, Sadee W, Costa T: Differential expression of alpha-subunits of G-proteins in human neuroblastoma-derived cell clones. *FEBS Lett* 224:43, 1987
9. Kumar S, Steward JK, Waghe M, Pearson D, Edwards DC, Fenton EL, Griffith AH: The administration of the nerve growth factor to children with widespread neuroblastoma. *J Pediatr Surg* 5:18, 1970
10. Levi-Montalcini R, Angeletti PU: Nerve growth factor. *Physiol Rev* 48:534, 1968
11. Marchetti D, Perez-Polo JR: Nerve growth factor receptors in human neuroblastoma cells. *J Neurochem* 49:475, 1987
12. Marsden HB, Steward JK: *Tumors in children*. Berlin, Springer-Verlag, 1968, chap 6
13. Mill JF, Chao MV, Ishii DN: Insulin, insulin-like growth factor II, and nerve growth factor effects on tubulin mRNA levels and neurite formation. *Proc Natl Acad Sci USA* 82:7126, 1985
14. Mobbley WC, Server AC, Ishii DN, Riopelle RJ, Shooter EM: Nerve growth factor (third of three parts). *N Engl J Med* 197:1211, 1977
15. Recio-Pinto E, Ishii DN: Effects of insulin, insulin-like growth factor-II and nerve growth factor on neurite outgrowth in cultured human neuroblastoma cells. *Brain Res* 302:323, 1984
16. Recio-Pinto E, Lang FF, Ishii DN: Insulin and insulin-like growth factor II permit nerve growth factor binding. *Proc Natl Acad Sci USA* 81:2562, 1984
17. Rettig WJ, Thomson TM, Spengler BA, Biedler JL, Old LJ: Assignment of human nerve growth factor receptor gene to chromosome 17 and regulation of receptor expression in somatic cell hybrids. *Somat Cell Mol Genet* 12:441, 1986
18. Reynolds CP, Perez-Polo JR: Induction of neurite outgrowth in the IMR-32 human neuroblastoma cell line by nerve growth factor. *J Neurosci Res* 6:319, 1981
19. Ross AH, Grob P, Bothwell M, Elder DE, Ernst CS, Marano N, Ghrist BFD, Slemp CC, Herlyn M, Atkinson B, Koprowski H: Characterization of nerve growth factor receptor in neural crest tumors using monoclonal antibodies. *Proc Natl Acad Sci USA* 81:6681, 1984
20. Sonnenfeld KH, Ishii DN: Fast and slow nerve growth factor binding sites in human neuroblastoma and rat pheochromocytoma cell lines:

- relationship of sites to each other and to neurite formation. *J Neurosci* 5:1717, 1985
21. Sonnenfeld KH, Ishii DN: Nerve growth factor effects and receptors in cultured human neuroblastoma cell lines. *J Neurosci Res* 8:375, 1982
 22. Spinelli W, Sonnenfeld KH, Ishii DN: Effects of phorbol ester tumor promoters and nerve growth factor on neurite outgrowth in cultured human neuroblastoma cells. *Cancer Res* 42:5067, 1982
 23. Stach RW, Lyons CR, Perez-Polo JR: Characteristics of partially purified nerve growth factor receptor. *J Neurochem* 49:1280, 1987
 24. Waghe M, Kumar S, Steward JK: Nerve growth factor in human sera. *J Pediatr Surg* 5:14, 1970