Neuroblastoma is perhaps the most fascinating and enigmatic of childhood tumors. This tumor may regress spontaneously in infants, grow relentlessly in older children, or differentiate into benign ganglioneuromas. Much of the effort to understand these diverse clinical behaviors has focused on the identification of the genetic rearrangements that characterize subsets of neuroblastomas. The most commonly identified abnormalities include amplification of the N-myc proto-oncogene, deletion of the short arm of chromosome 1, and allelic loss of the long arm of chromosome 14 (1-11). Also, hyperdiploidy, as identified by cytogenetic analysis or flow cytometric analysis of DNA content, is associated with a favorable outcome in infants (7,8,12-14). However, with the exception of N-myc, the critical genes affected by these abnormalities are not known.

Nerve growth factor (NGF) is a protein that promotes survival and induces differentiation in developing sympathetic neuroblasts, the presumed precursors of neuroblastomas. NGF acts through a specific receptor, and the nature of this receptor has been recently identified. The primary component is the glycoprotein gp140TRK-A, the product of the TRK-A gene (15-17). This transmembrane tyrosine kinase may function either alone or in a complex with another transmembrane glycoprotein called gp75LNGFR, encoded by the LNGFR gene (18,19). Nevertheless, expression of gp140TRK-A is clearly required for biological activity. Prior studies of NGF receptor expression in neuroblastomas have focused on gp75LNGFR, which until recently was the only known component of the NGF receptor (20-23). However, since the discovery of TRK-A and gp140TRK-A, a re-examination of the expression, function, and significance of the NGF receptor in neuroblastomas has been initiated.

The important manuscript by Suzuki et al. (24) draws attention to the aggressive nature of neuroblastomas that do not express the NGF receptor. Indeed, in a prior study by Nakagawara and colleagues (25), we showed that TRK-A expression was inversely related to N-myc amplification and was associated with a poor outcome. The study by Suzuki et al. extends these findings by showing that low TRK-A mRNA expression is also associated with disease progression in tumors without N-myc amplification. The results of their study suggest that TRK-A expression is a very powerful prognostic marker that is complementary to assessment of N-myc copy number. The study also demonstrates that LNGFR expression does not have prognostic value, further supporting the biological importance of TRK-A expression. Finally, Suzuki et al. show that there were no gross rearrangements of the TRK-A gene, implying that the lack of expression may be regulated by transcription and may reflect the stage of differentiation of the tumor cells. An independent study by Nakagawara and colleagues (26) supports the importance of TRK-A expression and N-myc amplification as powerful and complementary prognostic markers for neuroblastomas. These studies are particularly important because of the potential role of the NGF receptor in regulating growth, differentiation, or regression of neuroblastomas. Normal sympathetic neuroblasts from newborn animals survive in culture in the presence of NGF, but they undergo programmed cell death in its absence (27,28). The failure to express the NGF receptor TRK-A may be an early step in the tumorigenesis of immature neuroblasts, rendering them unable to respond to the normal developmental signal to differentiate or die. As such, they may continue to grow in an embryonic mode, sustaining subsequent genetic mutations or rearrangements that ultimately lead to complete malignant transformation. Indeed, these tumors may be arrested at an early developmental stage, and they may neither require NGF for survival nor differentiate in its presence. This may explain in part the particularly aggressive behavior of TRK-A-negative tumors, many of which have N-myc amplification (24-26). On the other hand, it is possible that neuroblastomas expressing the NGF receptor may be susceptible to differentiation or regression, depending on the presence or absence of NGF or another neurotrophic factor in the environment.

TRK-A expression also serves as a potential mechanism to at least partly explain the favorable outcome associated with hyperdiploid tumors in infants and the poor outcome associated with N-myc amplification in infants and older children. In the studies by Nakagawara and colleagues (25,26), a subset of the tumors had been identified by mass screening, a population that characteristically has a hyperdiploid karyotype (or DNA content) and a favorable outcome (29). All of these tumors had very high TRK-A expression (25,26). Conversely, the expression of TRK-A is essentially absent in neuroblastomas with N-myc amplification (24-26). Thus, the presence or absence of TRK-A expression provides a mechanistic link between these two seemingly unrelated genetic markers.

Interestingly, the TRK-A gene is but one of a family of genes encoding neurotrophin receptors that includes TRK-B,
the receptor for brain-derived neurotrophic factor (30), and TRK-C, the receptor for neurophin-3 (31). Indeed, these or other neurotrophic factors and their receptors may play an important role in the regulation of survival, growth, or differentiation of neuroblastomas and their precursors. A better understanding of the expression and function of the neurotrophic factor receptor pathways promises to provide tremendous insights into the biology of neuroblastoma and, in particular, its propensity to differentiate or regress spontaneously. More importantly, however, these pathways may prove to be attractive targets on which to focus future therapeutic approaches.

References


Notes

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