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News and Perspectives

Neuroblastoma—A Model Disease for Childhood Cancer

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Neuroblastoma is the most common extracranial solid tumor in childhood and the most frequently diagnosed malignancy during infancy. It is rare in adults and more than 96% of patients diagnosed with neuroblastoma are less than 10 years of age.[1] Most neuroblastoma develops sporadically and only 1–2% of newly diagnosed neuroblastoma cases have a family history.[2] It accounts for 5–6% of all childhood cancer and there are 20–30 new cases per year in Taiwan (data from Childhood Cancer Foundation, R.O.C., unpublished data).

This embryonic neoplasm derives from neural crest precursor cells of the peripheral sympathetic nervous system and usually arises in a paraspinal sympathetic ganglion or the adrenal gland.[3] The histological composition of neuroblastoma varies from primitively undifferentiated neuroblasts without discernible neuropils to mature ganglion cells with abundant neuropils.[4] The clinical behavior of neuroblastoma is also remarkable, with a broad spectrum, and can be categorized into three distinct patterns: (1) life-threatening progression; (2) spontaneous regression; and (3) spontaneous maturation to benign ganglioneuroma. Therefore, neuroblastoma is a heterogeneous tumor with diverse biological characteristics, which range from highly malignant tumors with very poor outcomes to the most benign ganglioneuroma or neuroblastoma with spontaneous regression and hence favorable prognosis.[3]

The heterogeneous clinical behavior of neuroblastoma is usually closely associated with heterogeneous genetic changes and biological features.[1] Somatic changes, such as gain or loss of alleles, and activation of oncogenes, or variations in tumor-cell ploidy have been shown to be crucial in the development of sporadic neuroblastoma.[1] According to the accumulated research data on the genetics of neuroblastoma, there are at least two genetic subsets of neuroblastoma, which are highly associated with clinical behavior. The first genetic type of neuroblastoma has a hyperdiploid or near-triploid karyotype, with very few or no cytogenetic rearrangements. The nerve growth factor receptor TrkA is usually highly expressed on this type of tumor, and leads neuroblastoma cells to apoptosis or differentiation, depending on the presence of nerve growth factor. Patients with this type of neuroblastoma are usually less than 1 year of age with localized disease, and have a very good outcome.[1] This type of neuroblastoma is

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categorized as a low-risk disease upon treatment.[5] In contrast, the other genetic type of neuroblastoma has a near-diploid or tetraploid karyotype with structural aberrations, which might affect the oncogenes or tumor suppressor genes on chromosomes 1p, 11q and 17q, including *MYCN* gene.[1] The most aggressive subset in this type of neuroblastoma has *MYCN* amplification, and usually loss of heterozygosity of chromosome 1p. Brain-derived neurotrophic factor and its receptor TrkB are frequently expressed on this type of tumor, and presumably form an autocrine survival pathway that confers a selective advantage on neuroblastoma cells. Patients with this type of neuroblastoma are usually more than 1 year of age with an advanced disease stage, and have a very poor outcome.[1] This type of neuroblastoma is categorized as a high-risk disease upon treatment.[5] Therefore, biological characteristics are crucial for the prognosis of neuroblastoma, in addition to traditional clinicopathological factors of age, tumor stage, and tumor histology.

The current treatment for neuroblastoma is risk-adapted according to the classification system established by the International Neuroblastoma Risk Group.[5] This system combines various clinicopathological and biological prognostic factors, including patient age, disease stage, tumor histology, and biomarkers including *MYCN* amplification, 11q aberration, and tumor ploidy, for risk-group assignment and treatment stratification.[6] In addition to chemotherapy intensity, molecular biomarkers might also affect the surgical decisions in neuroblastoma treatment.[7] Furthermore, we recently identified several biomarkers with prognostic significance in neuroblastoma,[8] including calreticulin, glucose-regulated protein 78, and glucose-regulated protein 75. These markers further stratify neuroblastoma patients for more appropriate therapeutic strategies, and might serve as a target for the treatment of neuroblastoma in the future.

The conventional treatment for patients with high-risk neuroblastoma consists of intensive cytotoxic chemotherapy, external beam radiotherapy, or radical surgery with or without autologous bone marrow transplantation.[3] Nevertheless, patients with high-risk neuroblastoma still have a very poor prognosis with a long-term survival of < 40%.[3] As more biological characteristics of neuroblastoma are identified, more therapies according to these biological targets are developed for clinical practice. For example, differentiation therapy using 13-*cis*-retinoic acid has been shown to improve outcome of high-risk neuroblastoma after bone marrow transplantation, with only minimal toxicity.[1] Radioactive meta-iodobenzylguanidine is useful for specific diagnostic imaging and targeted radiotherapy of neuroblastoma.[3] Disialoganglioside-targeted monoclonal antibodies have been assessed in early phase trials, and are being studied with synergistic cytokines in phase III trials in newly diagnosed neuroblastoma patients.[3] *ALK* has recently been identified as a major familial neuroblastoma predisposing gene.[2] However, active mutations of *ALK* are not only in germline, but are also somatically acquired in 6–12% of sporadic cases of neuroblastoma.[2,9] These findings suggest *ALK* as a tractable therapeutic target in neuroblastoma.[2,9] Other biologically based therapies for neuroblastoma, such as induction of apoptosis, inhibition of angiogenesis, metronomic therapy, and inhibition of tyrosine kinase, are also under development, which might potentially lead to a more specific but less toxic treatment in the future.[1,3]

Finally, neuroblastoma is an embryonic neoplasm that is derived from neural crest precursor cells; therefore, its cells possess the properties of further differentiation as well as neuronal characteristics. Neuroblastoma might serve as a model for research on the developmental biology of the nervous system as well as neurological diseases. For example, neuroblastoma cells have been used as a tool for *in vitro* validation of many studies that have focused on Alzheimer's or psychological disease.[10] The crosstalk between different fields of research can bring unexpected practical applications. Recently, we have demonstrated that a γ-secretase inhibitor, originally used in the treatment of Alzheimer's disease, was also effective in reducing tumor size of neuroblastoma in an animal study.[11] Furthermore, neuroblastoma might also

serve as a model disease for research into other childhood cancers, because genetic and biological analysis of neuroblastoma cells might provide crucial information for guidance of optimal patient management.[1] A single array-based platform for genetic and molecular profiling that can reliably and accurately detect allelic gains or losses, as well as *MYCN* amplification, and tumor ploidy of neuroblastoma at diagnosis, can be easily reproduced between various cooperative groups or countries.[6] This could help to identify genetic signatures of neuroblastoma with prognostic and pathogenetic significance, and identify new molecular targets for novel therapies.

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