Neuroblastoma (NBL)

- Evaluation of TRPA1 as a Therapeutic Target in MYCN-Amplified Neuroblastoma
- The people behind the papers - Anna Philpott and William Beckman
- Extracellular Matrix Topography Drives Adrenergic to Mesenchymal Transition in Neuroblastoma
- The Role of Serine-Threonine Kinase Receptor-Associated Protein (STRAP) Signaling in Cancer
- Functional Expression of NMDA Receptors in SH-SY5Y Neuroblastoma Cells Following Long-Term RA/BDNF-Induced Differentiation
- Hyperoside flavonoids protect against malathion-induced mitochondrial toxicity in the differentiated SH-SY5Y cells
- Peripheral neuroblastic tumors: tumor biology and its implications for risk stratification
- Cancer Stem Cell Characterization in Olfactory Neuroblastoma Tissue

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Neuroblastoma, an embryonal cancer of neural crest arise from the sympathetic ganglion [1].

Shows metastases frequently at diagnosis.

Sources of cerebral mets in peds:

Neuroblastoma

Rhabdomyosarcoma.

Wilm's tumor.

May occur anywhere in the sympathetic nervous system, most commonly from adrenal gland (40%), followed by sympathetic ganglia of thoracic (15%), cervical (5%) and pelvic regions (5%). Neoplasms under this rubric include:

1. neuroblastomas: the most undifferentiated and aggressive in this group.

2. ganglioneuroblastomas

3. ganglioneuromas.

Olfactory neuroblastomas are called esthesioneuroblastomas.

Delloye-Bourgeois and colleagues demonstrate that neuroblastoma cell lines and patient-derived xenografts engraft and adopt a metastatic program in chick embryos. They identify Sema3C as a candidate switch that regulates metastatic spread [2].

Epidemiology

Is the most malignant tumor in children and most common solid tumor in infants accounting for 8-10% of all childhood malignancies (about 8.7 million/year). It affects primarily children younger than 10 years of age. About 50% are below the age of 2 years. It occurs more frequently in boys than in girls (1.2:1). It originates from the neural crest cell, which normally gives rise to the adrenal medulla

and sympathetic ganglia anywhere from the neck to the pelvis. It occurs in the abdomen in about 70% of cases (45% in adrenal medulla and 25% in sympathetic ganglia) [3].

Malignant tumors that have increased frequency in neurofibromatosis: neuroblastoma, ganglioglioma, sarcoma, leukemia, Wilm's tumor, breast cancer [4].

Pathology

NBL consists of nests of neuroblasts (undifferentiated small round cells) separated by fine fibrovascular septa (stroma) and showing Rosette formation in about one-third of cases. In about 5-10% of cases, some neuroblasts show differentiation into mature ganglion cells and the tumor is classified as ganglioneuroblastoma; however, in adolescents and young adults, the tumor is formed of mature ganglion cells separated by collagenous stroma and called ganglioneuroma and this is the most benign type of NBL. NBL and ganglioneuroblastoma were classified by Shimada and recently by International Neuroblastoma Pathology Classification into favorable and unfavorable histology tumors according to the degree of neuroblasts differentiation and stromal development (stroma-rich and stroma-poor) [5].

Amplification of the MYC family member, MYCN, is found in ~25% of cases and correlates with high-risk disease and poor prognosis. Currently, amplification of MYCN remains the best-characterized genetic marker of risk in neuroblastoma. This article reviews roles for MYCN in neuroblastoma and highlights recent identification of other driver mutations. Strategies to target MYCN at the level of protein stability and transcription are also reviewed [6].

Patients with NBL may show genetic abnormalities in the form of deletion in the short arm of chromosome one and amplification of genes of chromosome two (called N myc gene amplification) and this is considered a poor prognostic factor of the disease [7].

Clinical features

Neuroblastoma clinical features.

Diagnosis

Neuroblastoma Diagnosis

Treatment

Treatment of NBL is a multimodality therapy composed of surgery, chemotherapy, and radiotherapy either in combination or separate depending on disease stage, patient age, genetic abnormalities, tumor biology, and histological classifications [8] see esthesioneuroblastoma.

Arsenic trioxide (As2O3), known as pi-shuang and the most toxic compound in traditional Chinese medicine, has been used as an antitumor agent for thousands of years. Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a natural phenol that has significant anti-bacterial, anti-fungal and antiaging activities. A study of Yen et al. from Taichung, Taiwan, aimed to examine the combined anticancer effects of As2O3 and resveratrol against human neuroblastoma SK-N-SH cells, and elucidate the underlying intracellular signaling.

SK-N-SH cells were treated with an extremely low-dose (2-4 μM) of As2O3 alone or combined with 75 μg/ml resveratrol for further comparisons. Cell viability, apoptotic signaling as well as synergistic cytotoxic effects were estimated using the MTT assay, microscopy observation, flow cytometric analysis for loss of mitochondrial membrane potential (MMP) and reactive oxygen species (ROS), and typical quantitative western blotting analysis. Student's t-test, and one- and two-way analysis of variance (ANOVA) were used for examination of significant differences.

The combined treatment was more effective than single treatment of As2O3 or resveratrol alone in suppressing cell viability, which correlated with the elevation of ROS levels. The intracellular mechanisms of cytotoxicity of As2O3 plus resveratrol were revealed as ROS accumulation and relative decrease of MMP, leading to activation of caspase-3 and -9, but not of caspase-1, -7 and-8. Combination treatment reduced the expression of B-cell lymphoma 2 (BCL2), BH3 interacting domain death agonist (BID), and BCL-x/L.

Combined treatment at extremely low concentration of two agents from natural products, As2O3 and resveratrol, has high potential as a cocktail of anticancer drugs for neuroblastoma [9].

Yang et al tested antitumor effects of sorafenib (≤ 10 μM) on four human neuroblastoma cell lines, CHLA255, CHLA171, CHLA90 and SK-N-AS. Sorafenib inhibited cell proliferation and induced apoptosis of neuroblastoma tumor cells in a dose-dependent manner. Sorafenib inhibited phosphorylation of Signal Transducer and Activator of Transcription 3 (STAT3) proteins at Tyr705 in these cells, associated with inhibition of phosphorylated JAK2, an upstream kinase that mediates STAT3 phosphorylation. Expression of a constitutively-activated STAT3 mutant (pSTAT3-C) partially blocked the antitumor effects of sorafenib on neuroblastoma cells. Sorafenib also inhibited the phosphorylation of STAT3 induced by IL-6 and sphingosine-1-phosphate (S1P), a recently identified regulator for STAT3, in these tumor cells. Moreover, sorafenib downregulated phosphorylation of MAPK (p44/42) in neuroblastoma cells, consistent with inhibition of their upstream regulators MEK1/2 [10].

Outcome

Neuroblastoma outcome.

Research

MYCN amplification is tightly associated with the poor prognosis of pediatric neuroblastoma (NB). The regulation of NB cell death by MYCN represents an important aspect, as it directly contributes to tumor progression and therapeutic resistance. However, the relationship between MYCN and cell death remains elusive. Ferroptosis is a newly identified cell death mode featured by lipid peroxide

accumulation that can be attenuated by GPX4, yet whether and how MYCN regulates ferroptosis are not fully understood.

Lu et al. reported MYCN-amplified NB cells are sensitive to GPX4-targeting ferroptosis inducers. Mechanically, MYCN expression reprograms the cellular iron metabolism by upregulating the expression of TFRC, which encodes transferrin receptor 1 as a key iron transporter on the cell membrane. Further, the increased iron uptake promotes the accumulation of labile iron pool, leading to enhanced lipid peroxide production. Consistently, TFRC overexpression in NB cells also induces selective sensitivity to GPX4 inhibition and ferroptosis. Moreover, they found that MYCN fails to alter the general lipid metabolism and the amount of cystine imported by System Xc(-) for glutathione synthesis, both of which contribute to ferroptosis in alternative contexts. In conclusion, NB cells harboring MYCN amplification are prone to undergo ferroptosis conferred by TFRC upregulation, suggesting that GPX4-targeting ferroptosis inducers or TFRC agonists can be potential strategies in treating MYCN-amplified NB [11)].

Iniguez et al. used bromodomain and extra-terminal domain (BET) inhibition in neuroblastoma as a prototype to model resistance to chromatin modulatory therapeutics. Genome-scale, pooled lentiviral open reading frame (ORF) and CRISPR knockout rescue screens nominated the phosphatidylinositol 3-kinase (PI3K) pathway as promoting resistance to BET inhibition. Transcriptomic and chromatin profiling of resistant cells revealed that global enhancer remodeling is associated with upregulation of receptor tyrosine kinases (RTKs), activation of PI3K signaling, and vulnerability to RTK/PI3K inhibition. Large-scale combinatorial screening with BET inhibitors identified PI3K inhibitors among the most synergistic upfront combinations. These studies provide a roadmap to elucidate resistance to epigenetic-targeted therapeutics and inform efficacious combination therapies [12)].

Case series

A retrospective single-center analysis of all neurosurgical strategies used in the treatment of intracerebral metastases in neuroblastoma patients.

Between 2009 and 2017, 237 pediatric patients (94 girls, 143 boys) with a mean age of 39 months at diagnosis were treated for neuroblastoma. Five (2.1%) of the 237 patients had a neurosurgical procedure for intracerebral metastases. The metastases occurred a mean of 46 months after initial diagnosis. All of these patients had neuroblastoma stage 4. Indications for surgery were recurrent metastases after initial successful oncological treatment or progression of the metastases under oncological treatment as well as deterioration of neurological function. Intraoperatively, the tumor usually had a distinguishable dissection plane but was infiltrative to adjacent nerves in some spots. Mean overall survival after the neurosurgical procedure was 22 months. Furthermore, in another 3 patients, a neurosurgical procedure was done for an intracranial but extracerebral metastases.

Neurosurgical procedures for intracerebral metastases in neuroblastoma patients are rare and were performed in 2.1% of patients in the present study. Intracerebral metastases occurred during disease progression, and the prognosis after surgery was very limited. The main indications for surgery were rapid neurological deterioration or recurrence of the metastases after initial successful oncological treatment. Intraoperatively, the metastases usually had a distinguishable dissection plane from the normal brain tissue [13)].

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