Cancer Research Center Hotline

Targeting Oncogene Expression in a Childhood Cancer

Matthew C. Tuthill, PhD Junior Researcher Cancer Research Center of Hawaii

Randal K. Wada, MD Associate Researcher Cancer Research Center of Hawaii

Neuroblastoma is a common solid tumor of young children

Neuroblastoma is a childhood cancer originating in pluripotent nerve cells from the neural crest that normally give rise to the postganglionic sympathetic nervous system. It is the most common extra-cranial tumor in infants, with 600 new cases diagnosed in the United States annually. In children neuroblastoma represents 10% of all tumors, but is responsible for more than 15% of pediatric cancer deaths.

One reason for this discrepancy is that in the majority of cases, the tumor has already metastasized by the time of diagnosis. Unlike other forms of childhood cancer, advances in therapy have only recently begun to yield an increase in survivorship for neuroblastoma patients with the more aggressive forms of disease. Since most neuroblastoma patients are infants and young children, the need for less toxic yet more effective therapy is especially important. Some of the major challenges that are being addressed are how to balance the effectiveness of treatment and side effects from radiation/ chemotherapy with long-term patient health. New approaches capitalize on the emerging insights we have gained into the biology of this tumor.

Neuroblastoma can regress, or mature to a benign form

One of the most remarkable and unique features of neuroblastoma is the occurrence of complete spontaneous regression, or differentiation. In fact, despite its aggressive behavior in the majority of patients, neuroblastoma exhibits the highest rate of spontaneous regression of any human malignancy. Tumor regression is most commonly observed in infants, while tumors in older patients can differentiate into benign ganglioneuroblastoma or ganglioneuroma. Neuroblastoma thus provides an interesting model system for the development of differentiation therapy that could be less debilitating than conventional chemotherapy, yet increase survivorship.

Retinoic acid turns off the N-myc oncogene, a key step in inducing differentiation

Experimentally, cultured neuroblastoma cells can be induced to differentiate by a number of agents, including retinoic acid,

phenylacetate, gamma interferon, and vitamin D. An early, key event in the differentiation process, both in tumor cells exposed to retinoic acid and in normal fetal neuroblasts during neuronal development, is a decrease in N-myc oncogene expression. In turn, Nmyc downregulation immediately precedes growth arrest, and is followed by morphologic and biochemical maturation (neurite extension, neurotransmitter biosynthesis, nerve impulse conduction). In patient tumors, activation of the N-myc oncogene is associated with aggressive disease, including tumor metastasis, resistance to chemotherapy, and rapid tumor progression. In the laboratory, if N-myc downregulation is prevented by the introduction of exogenous N-myc genes, retinoic acid-induced differentiation can be blocked. Conversely, decreasing N-myc expression by specific anti-sense oligonucleotides induces tumor cell differentiation even in the absence of any drugs. Thus, regulation of N-myc by agents such as retinoic acid appears to be an important factor in determining the biological behavior of this tumor.

Retinoic acid improves patient survival

Clinically, differentiation therapy with retinoic acid has been shown to have its greatest benefit in the setting of minimal residual disease, following gross tumor debulking by chemotherapy, surgery, autologous stem cell transplant, and radiation therapy. Patients treated with retinoic acid have a significantly higher survival rate than those receiving the same therapy without retinoic acid. With multi-modal conventional therapy, stem cell transplant, and retinoic acid, the current 5-year disease-free survival rate has increased to approximately double that of historical controls.

Retinoic acid resistance is associated with persistent N-myc expression

While new findings on the clinical usefulness of retinoic acid represent encouraging progress, a significant number of children nonetheless suffer from tumor relapse, and survival in patients with disease progression is dismal. Based on cell culture and animal models, a potential cause of failure may be the development of retinoic acid resistance, involving loss of the ability to downregulate N-myc expression.

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Understanding the molecular regulation of N-myc transcription

Part of our work at the Cancer Research Center of Hawaii has focused on gaining an understanding of the molecular switch that turns the N-myc gene off in response to treatment with retinoic acid. A decrease in N-myc expression appears to be necessary for differentiation to proceed. Our data suggest that mutations in the control region, or promoter, of the N-myc gene result in the recruitment of alternative transcription factors. N-myc mRNA production is thus driven by a different set of regulatory proteins than in the normal promoter with wild type sequence. Unlike the usual proteins, those associating with mutant promoters may be unaffected by retinoic acid, so that treated cells bearing these mutations can no longer shut the N-myc gene off and continue on with the differentiation program. Persistent N-myc expression, even in the face of retinoic acid, would confer a growth advantage on these cells, and contribute to their chemotherapy resistance. Clinically, such factors may underlie the process of tumor relapse and disease progression.

Clinical applications of mechanism-based research

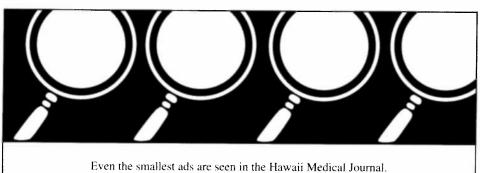
Through determining the mechanism of N-myc downregulation by retinoic acid we hope to derive a set of molecular diagnostics that will allow us to examine tumor DNA for significant promoter mutations, and use this information to gauge patients' prognoses with respect to their potential responsiveness to retinoic acid. Rather than using retinoic acid as the default drug to deal with minimal residual disease, patients at risk for treatment failure could be triaged to receive new investigative therapies. Identification of the alternate proteins that mediate N-myc transcription in retinoic acid-resistant cells may suggest agents that would be effective even on N-myc genes with mutant promoters. Ultimately these drugs could be used in conjunction with retinoic acid, much like we currently combine different conventional chemotherapeutic agents. However, an important distinction would be that the goal of this combination differentiation therapy would be to effect cure by "rehabilitating" cancer cells, rather than killing them.

Therapy rooted in tumor cell biology, not tumor cell toxicity

Molecular, mechanism-based approaches such as this are part of a newly emerging treatment paradigm rooted in a basic understanding of tumor biology, and should increase treatment efficacy while reducing its toxicity. While this is especially valuable in the therapy of young children, lessons learned in neuroblastoma may one day benefit adult patients with lymphomas and small cell lung carcinomas, since these tumors are also driven by oncogenes of the myc family, including N-myc. For more information, please visit the Cancer Research Center's website at www.crch.org.

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