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Pathology and Advancing Technologies Referring to Neuroblastoma

Author: Morgan Nipp
Major: Biochemistry and Molecular Biology
Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA

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The uncontrolled division is what we know as cancer. Cancer, as we know, can grow anywhere and everywhere within the body, and impair the function of organs, nerves, and muscles. Neuroblastomas are a rare, solid, very specific type of cancer that targets sympathetic nervous system nerve cells. Neuroblastomas develop within immature nerve cells known as neuroblasts. Neuroblastomas can begin impairing the sympathetic nervous system of children as young as in the embryonic stage. Neuroblastomas can be linked to abnormalities of genes, but that is not always the cause of the cancer. Out of every 100,000 cancer patients, 548.9 are between 40 and 64, 77.4 are between 15 and 39, and only 17.8 are younger than 15. Neuroblastomas are rare because this cancer usually affects children five years of age or below.

Introduction

Most cancers can be linked to a chemical carcinogen, physical carcinogen, or genetic mutation. Neuroblastoma is unlike most cancers. While it has been found mutations on the MYCN, ALK and PHOX2B genes can lead to neuroblastomas, that is not the case with every patient. According to New Approaches for Neuroblastoma Therapy, one-third of high-risk children have abnormal MYCN, ALK, and PHOX2B genes. Though, the other two-thirds of children that are considered high-risk have also undergone gene analysis, and no abnormalities were detected.

One of the earliest discoveries of a genetic marker for neuroblastomas was gene amplification of the MYCN gene. When amplified, two MYCN genes are one of the strongest indications of a late-stage diagnosis. Patients that are low risk and lack MYCN gene amplification do not progress to high risk. Anaplastic lymphoma kinase (ALK) encodes for tyrosine kinase receptors. ALK is the most common gene; when it becomes mutated, it leads to neuroblastomas. The discrepancy at the locus of ALK is found in almost all cases of familial neuroblastoma. Like the prognosis of the amplification of the MYCN gene, when ALK is mutated, there is a very high chance of late-stage diagnosis. The first gene linked to the cause of neuroblastoma was PHOX2B. The PHOX2B gene encodes a transcription factor that is essential for autonomic nervous system development. Scientists believe some

neuroblastomas arise from the irregular development of the neural crest due to mutations of the PHOX2B gene.

Since neuroblastomas are common in children too young to speak, identifying the symptoms isn't easy. Some symptoms, such as diarrhea, constipation, fatigue, unexplained weight loss, and loss of appetite are very common symptoms in many childhood illnesses. Other symptoms, including lumps or swelling in the abdomen, pain within the child's bones, drooping eyelids, pale skin, irregular body function, bumps under the skin that appear blue or purple, and trouble breathing, show a later stage but are more obvious.

If a child experiences multiple symptoms of neuroblastoma, proper diagnosis, and testing must be determined before a treatment plan is created. Blood and urine tests are performed to determine the levels of catecholamines. These are hormones produced by adrenal glands and show a sign of a neuroblastoma tumor within the body when they are in abundance. After blood and urine tests confirm high levels of catecholamines, imaging tests such as x-rays, ultrasounds, MRI, CT, MIBG scans, bone scans, or PET scans. Once an imaging exam is performed and shows a mass. A biopsy or bone marrow aspiration is collected. Once the tissue or bone sample is obtained, the sample is viewed under the microscope to determine if cancer cells are present. If cancer cells are present, they are evaluated further to determine the similarities compared to neuroblastoma.

Neuroblastoma is divided into groups based on the prognosis. The groups are low risk, intermediate risk, high risk, and recurrent risk. Children with low-risk neuroblastomas usually do not have to undergo very harmful treatment. Some neuroblastomas that are low risk can go away on their own, or they can be removed surgically. Children that fall in the intermediate category require surgery to remove the tumor and often undergo chemotherapy to ensure the tumor is completely out of the child's body. Furthermore, children that are in the immediate risk group require close monitoring to ensure the cancer does not reoccur. The high-risk group of children often undergo the most extensive cancer treatment plan, including but not limited to surgically removing the tumor, chemotherapy, radiation therapy, stem cell transplant, immunotherapy, and retinoid therapy. Children in the high-risk category are regularly tested to ensure the tumor has not grown or metastasized throughout the body. Children within the recurrent group experience a relapse of cancer that they have once overcome. These children are very closely monitored to ensure the cancer does not metastasize. Additionally, the treatment the second time usually involves a more extensive treatment plan.

Recent Progress

New technology, such as gene therapy, can play a vital role in the treatment of cancers such as neuroblastoma. This technology calls for identifying the entire genome sequence of an individual and targeting the genes that are mutated. Gene therapy is most successful when the targeting system allows efficient gene transfer. Viral vectors are often used in cancer treatment because of their high efficacy in gene transfer. Retroviral vectors were developed in the 1990s and have played a vital role in gene therapy within cancer research. A benefit of using retroviral vectors is their ability to integrate within the hosts genome allowing for a permanent gene transfer. The retroviral vector hosts the healthy genes and a promoter. Once the vector is incorporated into the target cells, the healthy and functional genes are utilized in the synthesis of DNA and the promoter is utilized to enhance the expression of the healthy gene. Another way gene therapy can benefit patients with neuroblastoma is by introducing CAR-T therapy. CAR- T therapy involves manipulating the patient's own immune system to express a chimeric antigen receptor (CAR) to bind on the surface of the cancer cells. Once the CAR-T cells bind to the surface of the cancer, cytokines are

released to destroy the cancer cells. Since gene therapy is a relatively new method of treatment, there is ongoing current research. Additionally, there are clinical trials to help explore the possibilities of success with this treatment method.

Discussion

In conclusion, neuroblastoma is a rare type of cancer that affects the nerve cells of the sympathetic nervous system, typically in children aged five and under. Neuroblastomas can arise from genetic mutations of genes such as MYCN, ALK, and PHOX2B. However not all cases are linked to gene abnormalities. Early diagnosis is challenging due to the lack of distinct symptoms, and proper testing must be performed to determine an effective treatment plan. Treatment plans vary based on the patient's prognosis group and may include surgery, chemotherapy, radiation therapy, stem cell transplant, immunotherapy, or radiation therapy. A current clinical trial is investigating the use of an experimental drug called lorlatinib. This drug works by inhibiting the ALK gene. Since ALK is found in many familial cases of neuroblastomas, this treatment could be very beneficial if proven to target the ALK gene and inhibit its functions. Gene therapy, utilizing viral vectors such as retroviral vectors, is a new technology that shows promise in the treatment of neuroblastomas. The identification of the entire genome sequence of an individual can help target specific genes and introduce healthy, properly functioning genes, improving the efficacy of treatment. Further research in gene therapy could lead to more effective treatments for neuroblastoma and other types of cancer.

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