4 Cancer Genetics and Molecular Oncology

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SUMMARY

Cancer is a genetic disease, but there are many different types of genetic changes found within a cancer cell. The study of relatively rare cancer predisposition disorders has provided crucial insights into basic mechanisms of cellular physiology and tumorigenesis. In this chapter, we review different mechanisms that result in an inherited predisposition to cancer, including chromosomal disorders, defects in imprinted genes, mutations in tumor suppressor genes, activation of oncogenes, and mutations in DNA repair genes. This research is now being accelerated through the Human Genome Project and high throughput analysis of the genetic changes found in cancer cells.

Key Words: Autosomal-dominant; autosomal-recessive; cancer susceptibility; deletions; DNA repair; imprinting; mutations; oncogenes; translocations; tumor suppressor genes.

INTRODUCTION

Overwhelming evidence demonstrates that cancer is the result of genetic changes in the DNA of the tumor cell. The mechanism of mutation and the impact of these somatic alterations on the growth of cancer cells make up the field of molecular oncology. In addition to mutational changes, a number of genes are deregulated in the cancer cell by epigenetic mechanisms including DNA methylation. Overall, the percentage of human cancers that is caused by a major inherited predisposition is low. That percentage varies with individual tumor types and is a composite of several different genetic factors. Despite their lower frequency, the ability to identify the genes mutated in these families has provided significant insight into the etiology of cancer in the general population. Our understanding of somatic mutations in cancer cells has relied heavily on identification of important genes through study of familial cases with subsequent research focused on mutations in these genes in sporadic cases (see Fig. 4-1). Key examples of the different forms of inherited predisposition to cancer will be reviewed.

Hereditary predisposition may include either genetic alterations that have been passed on to the individual from a parent or new mutations that occurred in the oocyte or sperm before fertilization. Therefore, hereditary predisposition to cancer is not always associated with a family history of the disease. For example, a de novo mutation in a cancer predisposing gene such as RB1 can result in healthy parents having a child with the hereditary form of retinoblastoma. In the case of new dominant mutations in genes that result in highly lethal tumors, there may not be a family history because the children with cancer do not live to reproduce. In these cases, the process of gene discovery can work in reverse (see Fig. 4-1). For example, in atypical rhabdoid tumors, it was found that the tumors frequently carry a cytogenetically visible deletion at chromosome 22q11.2. This harbors the hSNF5/INI-1 gene. Subsequently, children who carry a point mutation in this gene in their tumor were found to actually carry the mutation in all the cells in their body. These new dominant mutations presumably occur during the production of the egg or sperm before fertilization. This results in children with a cancer predisposition syndrome without an obvious family history. The identification of the gene by tumor cytogenetics allowed the uncovering of this syndrome. Thus, there may be other apparently sporadic cancers that could be the result of de novo constitutional mutations.

There are a variety of mechanisms that result in inheritance of cancer susceptibility. In this chapter, we will review examples of the major types including, constitutional chromosomal abnormality, Mendelian autosomal-dominant and autosomal-recessive patterns, and non-Mendelian inheritance. Non-Mendelian patterns include multigenic disorders, mutations in mitochondrial DNA, and imprinting errors. Imprinting refers to the fact that gene expression from a given gene may differ if the gene is on a chromosome inherited from the mother or father. Conversely, for any given tumor type there may be more than one mechanism that results in an inherited predisposition to that disorder. The most commonly cited example is Wilm’s tumor, a malignant cancer of the kidney frequently diagnosed in very young children. An increased risk of Wilm’s tumor can be the result of a chromosomal deletion, an autosomal-dominant disorder or a disorder of imprinting.

CONSTITUTIONAL CHROMOSOMAL ABNORMALITIES

Children with constitutional chromosomal abnormalities often present with many different medical problems including abnormalities in growth, multiple congenital anomalies (birth defects), and learning abnormalities. Constitutional chromosomal abnormalities are the result of abnormal number (i.e., aneuploidy) or structural rearrangements of chromosomes. Cells normally contain 46 chromosomes (i.e., 22 pairs of autosomes and the sex chromosome pair). In addition to their other medical problems, individuals with a constitutional chromosome problem may have an increased predisposition to cancer.
DOWN SYNDROME  Down syndrome (DS) is one of the most common chromosomal abnormalities in humans. It is the result of a child having three copies of chromosome 21 (trisomy 21). This increase in chromosome number typically results from an error in chromosome segregation during oogenesis. Thus, the child is usually the only person in the family with trisomy 21 and there is no structural abnormality in the three chromosome 21s present in the child. In addition to particular facial features and learning disabilities, it was noted quite early that children with DS have a strikingly increased predisposition to leukemia. By 5 yr of age approx 2% of children with DS will be diagnosed with leukemia. This is in contrast to approx 5/100,000 in the general population. Despite the fact that this association has been known for many years, we are still not certain which genes on chromosome 21 result in the increased leukemia risk. The completion of the sequencing of the entire chromosome 21 as part of the human genome project and large-scale expression studies of leukemia cells using microarray technology is facilitating this search. Children with DS also demonstrate another common feature of cancer predisposition syndromes, which is that they are increased risk for only certain cancer types, in spite of the fact that all cells of their body contain the extra chromosome 21. It is often the case that in inherited syndromes there are specific subtypes of cancer that show an increased predisposition. Again, scientists often do not have a molecular mechanism to explain this specificity. In the case of children with DS, they are particularly predisposed to an otherwise less common form of leukemia termed acute megakaryocytic leukemia (AMKL). AMKL is the result of malignant transformation of the megakaryocyte cell that produces platelets in the bloodstream. Outside of DS, AMKL is a very rare form of leukemia with a 400-fold increase of AMKL in children with DS. Clearly, the megakaryocyte is particularly sensitive to an extra copy of chromosome 21. Also, children with DS and AMKL show a different pattern of mutations in other genes within the cancer cell compared with other children with AMKL. In particular, the characteristic translocation between chromosomes 1 and 22 (t(1;22)[p13;q13]) is absent in children with DS and AMKL.

As we will discuss for other malignancies, the leukemogenic effect of trisomy 21 is also seen in children without DS. If one looks at the pattern of chromosomes from leukemia cells in children without DS, one frequently finds that the leukemia cell has acquired a third chromosome 21. Thus, if we can understand why children with DS have an increased risk of leukemia it may help us better understand leukemogenesis in the general population.

Despite the well-documented increase in the risk of leukemia in children with DS, several large-scale population studies have not found an increased risk of other cancers in children with DS. In particular, many common cancers, including breast cancer, were less frequent in the population of adults with DS. Again we see a specific relationship between trisomy 21 and leukemia risk even though all cells in the body contain an extra chromosome 21.

The reason why mutations in certain genes result in the development of cancer in only specific cell types is one of the remaining challenges in the field of cancer genetics.

STRUCTURAL CHROMOSOMAL ABNORMALITIES

Detection and Impact  The ability to detect the number and, subsequently, the overall shape of human chromosomes improved through the 1960s and 1970s. As these techniques improved it became possible to identify that deletions of certain portions of chromosomes were a frequent occurrence in human cancers. In a smaller number of patients, this deletion or chromosome loss is an inherited event and again may be associated with a specific pattern of birth defects. Over the last 20 yr, the technology has continued to improve. In particular, the development of fluorescently labeled DNA probes allowed researchers to identify chromosomes that appear normal in the microscope but are deleted for sequences that bind to the fluorescent probe. This technique is termed fluorescent in situ hybridization (FISH) and is in regular use in both clinical and research laboratories. Figure 4-2 demonstrates FISH analysis of leukemia cells demonstrating deletion of part of chromosome 5 that results in loss of the EGRI gene. Over the last several years, even newer methodologies are being developed to allow scientists to screen the entire genome of a normal or cancer cell for small areas of loss or gain. These methods combine the power of microchip arrays and fluorescent probes. Thus, we expect that our ability to detect clinically important deletions will increase exponentially in the next decade.

Deletions of a portion of a chromosome can result in the loss of several neighboring genes. The size of the deletion impacts how many of these genes are lost and how many different medical problems a patient may manifest. Chromosomal deletions may be de novo events or inherited from either parent.