Review Article

Mutations in genes onset the disease of cancer

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ABSTRACT

Cancer is a genetic disease, meaning it is caused by alterations in genes that control how our cells behave, mainly how they divide and grow. Proteins do a lot of the work in our cells, and genes provide the instructions for making them. Specific gene mutations can cause cells to escape standard growth regulators and turn cancerous. Some cancer-causing gene alterations, for example, enhance the synthesis of a protein that causes cells to proliferate. Others cause a malformed and hence non-functional form of a protein that typically repairs cellular damage to be produced. If the mutations are present in germ cells, the body's reproductive cells, we can inherit cancer-causing genetic abnormalities from our parents. Such mutations, known as germline mutations, can be identified in every cell of the offspring. Cancer-causing genetic mutations can also be acquired over ones lifespan due to cell division errors or exposure to carcinogenic compounds that damage DNA, such as some chemicals in tobacco smoke, and radiation, such as UV rays from the sun. Somatic (or acquired) alterations are genetic changes that occur after conception. Cancer cells, on average, exhibit more genetic alterations than healthy cells. However, each person cancer has a unique set of genetic mutations. Some of these alterations could be the effect rather than the cause of cancer. Additional alterations will occur as the malignancy progresses. Cancer cells may have diverse genetic alterations even within the same tumor.

KEY WORDS: Cancers; Cancer Genetics; Genetic Abnormalities

INTRODUCTION

An individual cell's growth and division are tightly controlled. When a cell's ability to divide is gone, it becomes tumorigenic. When a cell becomes malignant, it undergoes immortalization, transformation, and metastasis. The constant changes cause uncontrolled growth and interfere with the body's regular function. Although certain cancers are inherited, faults in DNA replication or exposure to carcinogens can cause mutations in somatic cells, which can then become malignant. Tumors are classed as benign or malignant based on their activity. Benign tumors are slow growing, vast masses encased in a fibrous capsule, whereas malignant tumors proliferate and spread to local tissue and distant locations.[1] The most practical classification of tumors is based on the tissue of origin and the kind of cell involved; for example, carcinoma is cancer developed from epithelium, which is the most well-known malignancy and accounts for more than 90% of tumors. Sarcoma develops in connective tissue, whereas leukemia develops in the bone marrow.[2] Tumor growth begins in the cell where a novel mutation confers a replication advantage over other cells, and the clone resulting from this cell expands at exponential rates in successive rounds. Following a series of mutations, a range of gene products is produced, which are essential for establishing the malignant phenotype. Carcinogenesis is a multistep process that begins with normal epithelial tissues and progresses through hyperplasia, dysplasia, carcinoma *in situ*, invasive carcinoma, and metastatic carcinoma.[3]

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CANCERS TYPES

Hereditary Cancer

Each cell, including somatic and germline in an individual's body, has a mutation or variation in some profoundly penetrant qualities, which is inherited. This is a usually uncommon cancer that records for generally 5–10% of every single firm tumor and a lesser level of hematological malignancies.

Sporadic

It includes only somatic cell mutations that represent over 90% of all cancer cases.

Familial Malignancies

Familial malignancies are brought about by ecological factors and abnormalities in various low penetrance genes. Contingent on where they happen, they represent 10–30% of all malignancies.[4]

GENETIC ABNORMALITIES IN CANCER

Numerical Abnormalities

The chromosome's unusual number and structures that are liable for mutations or flawed genes are among the hereditary abnormalities found in cancer cells. Aneuploidy refers to an unequal number of chromosomes. Hypodiploidy, which refers to a drop in the number of chromosomes, and hyperdiploidy, which refers to an increase in the number of chromosomes, are examples of numerical anomalies.[5]

Abnormalities in the Structure

Deletions, translocations, inversions, rearrangements, and amplifications are examples of structural chromosomal abnormalities. The deletion process involves the removal of a chromosomal portion from the set that may activate the tumor suppressor gene or the silencing of an oncogene.[6]

One chromosome separates and appends to an alternate non-homologous chromosome or another spot off a similar chromosome, bringing about translocation. Translocation is generally expected in lymphomas, sarcomas, and leukemias, with chronic myelogenous leukemia being the most notable chronic myeloid leukemia (CML). The oncogene breakpoint cluster region-Abelson murine leukemia (BCR-ABL) is framed when the long arm of chromosome 22 appends to chromosome 9 in CML.[7]

Inversion occurs when a piece of chromosome detaches and reinserts in the opposite orientation, resulting in either oncogene activation or tumor suppressor gene deactivation. The juxtaposition of the mixed-lineage leukemia gene with the clathrin assembly lymphoid myeloid leukemia gene, for example, causes acute myeloid leukemia in kids.[8]

Oncogenes

Oncogenes can turn healthy cells into cancerous cells. Proto-oncogenes are pre-mutated forms of oncogenes that promote cell proliferation, regulate differentiation, and reduce apoptosis. When mitogens and carcinogens are present, proto-oncogenes can transform into oncogenes.

Changes in the DNA or a regulatory space of a gene, such as a promoter, gene amplification, and chromosomal adjustment, for example, translocations, are the three processes engaged with turning a proto-oncogene into an oncogene.[9]

Translocation can activate oncogenes; one notable model is the BCR-ABL fusion gene connected to constant myelogenous leukemia.[10] The Philadelphia chromosome, which comes from a translocation between chromosomes 9 and 22, is known as BCR-ABL. This translation results in the uncontrolled creation of tyrosine, which leads to an excess of cell proliferation.[11]

Gene That Suppresses Tumors

A tumor suppressor gene is involved in fixing DNA errors, regulating apoptosis, and managing the pace of cell division, dependent on the requirement. The p53 gene is a notable tumor silencer gene that has been identified with leukemias, lymphomas, sarcomas, mind tumors, and bosom, colon, and lung carcinomas. When a tumor silencer gene is changed or inactivated, it stops working, bringing about the deficiency of the regulatory protein. This, when paired with the activation of an oncogene, has the potential to cause cancer.[12]

Gene Fusion

The formation of the fusion gene involved combining two different genes because of the structural faults in chromosomes that result in cancer through many routes. Overexpression, repression, shifting the location of a protein, and deleting the regulatory domains of specific genes are examples of these mechanisms. Gene fusion anomalies cause 20% of cancer in humans, but scientists can now interrupt the effects of these malfunctions thanks to technological advancements.[13]

Mutations in Passengers and Drivers

Driver mutations are essential for cancer cell survival and maintenance. At the point when a tumor has a few nonfunctional mutations that endure in the cancer cells, they are alluded to as "passenger mutations." These passenger mutations are found related to driver mutations every now and again, and they might be valuable in cancer diagnosis and exploration.[14]

Metabolic Enzymatic Pathway Mutations

Mutations in metabolic enzymatic pathways can offer a good climate for cancer cells to thrive. The cell can change over pyruvate to lactic corrosive in hypoxic conditions. However, this is an insufficient procedure for creating energy. Cancer cells, then again, can misuse this methodology effectively because they are isolated from the underlying stroma and blood veins.[15] An acidic microenvironment is framed because of expanded non-aerobic glycolysis, which is dangerous to normal cells. However, malignant cancer cells can adjust and endure the acid-activated cell toxicity.[16] During particular cell designated spots, abnormalities can likewise emerge during cell division and metabolism. When these designated spots become screwed up or glitch, the danger of the onset of cancer rises.

Metastasis

The ability of cancer cells to transfer to other parts of the body is known as "metastasis." Metastasis is responsible for around 90% of cancer fatalities, with the most prevalent sites of dissemination being the bone, liver, and lung.[17]

Angiogenesis

Angiogenesis is the process that involves the formation of new blood vessels. It is a critical step in cancer growth and spread. It's a multistep process controlled by angiogenic factors such as VEGF and HGF. Malignant cells can proliferate and metastasis when these growth factors and receptors are overproduced or become more sensitive.[18,19]

Apoptosis

Apoptosis is a typically controlled process of programmed cell death that occurs when a cell is damaged beyond repair or is no longer required for the body's function. When a cell's apoptotic pathway is disrupted, such as when the tumor suppressor gene P53 is turned off, the cell can grow and become cancerous.[20]

Resistant to Drugs

Tumors, like humans, are capable of evolving for survival, which leads to intrinsic or acquired resistance to chemotherapy. The term "intrinsic resistance" refers to the presence of resistance-mediating elements in the tumor during the course of treatment, and acquire resistance develops. Several investigations have found that overexpression of the P-glycoprotein and the multidrug resistance-associated protein is the key mechanism of resistance (MRP).[21]

Tumor Classification and the Cancer Genome

Malignant tumors have traditionally been classed based on the site of origin and, in some cases, morphology. Many modern genomic analyses are possible to reveal the reasons for heterogeneity in cancers coming from a variety of organs in the body, thank to technological advancements. With all of this information, we can potentially rethink the way we classify cancers with new classification and nomenclature. It will also give researchers a better knowledge of biology, prognosis, and therapy choices for new malignant cancers.[22]

Cancer Genetics' Molecular Basis

On the basis of histology, site of origin, and biological behavior, cancer diagnostics are divided into several categories. With the advancement of molecular technology, researchers and physicians have been able to use it in cancer diagnosis and treatments with more success and reduced danger of toxicity.

CML

CML is unrestrained granulocyte production. In CML patients, Nowell and David Hungerford discovered a tiny shared chromosome.[23] The translocation between chromosomes 9 and 22 is known as the Philadelphia Chromosome.[24] A fusion gene known as BCR-ABL was created as a result of changes in the molecular makeup. BCR-ABL functions as an oncogene, causing constitutive tyrosine kinase production and bulk creation of white blood cells. Imatinib, a BCR-ABL tyrosine kinase inhibitor, is a highly effective treatment for chronic CML and has established the bar for genotype-targeted therapy for other cancers.[25]

Breast Cancer

The human epidermal growth factor receptor 2 gene and estrogen receptor 2 gene (ER2) are two mutations that are widely observed in clinical settings (ER). They result in unrestricted proliferation and resistance to apoptosis. In the presence of estrogen, ER is activated, and the oncogenes c-MYC and cyclin D1 stimulate transcription.[26] Furthermore, breast cancer susceptibility gene 1 and 2 are the two most common genes involved for breast cancer inheritance (BRCA1 and BRCA2). BRCA1 and BRCA 2 are tumor suppressor genes that repair DNA breaks and are found in approximately 80% of family breast cancer cases. The presence of these genes increased the risk of cancer and accelerated the beginning of the disease.[27]

Colon Cancer

In around 10%–25% of instances, colorectal neoplasms are hereditary. Familial adenomatous polyposis is a tumor suppressor gene mutation that causes thousands of polyps to grow in a person as early as their 20s and can progress to cancer.[28] Hereditary non-polyposis colorectal cancer, which is caused by a mutation in the mismatch repair genes, is another condition that progresses to carcinoma. The tumor

suppressor gene p53 and the KRAS gene are two additional alterations that are regularly encountered. KRAS is important for cellular proliferation, while p53 is responsible for cellular death.[29] KRAS is detected in around one-third of all human malignancies.[30]

REFERENCES

1. Anand P, Kunnumakkara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, *et al*. Cancer is a preventable disease that requires major lifestyle changes. Pharm Res 2008;25:2097-116.
2. Agarwal SP, Rao YN, Gupta S. Fifty Years of Cancer Control in India, Ministry of Health and Family Welfare Government of India; 2002.
3. Campbell K. The Genetic Basis of Cancer. London: Nursing Time; 2000.
4. Koul B. Types of Cancer. Berlin, Germany: Springer; 2019.
5. Holland AJ, Cleveland DW. Boveri revisited: Chromosomal instability, aneuploidy and tumorigenesis. Nat Rev Mol Cell Biol 2009;351:478-87.
6. Dong JT. Chromosomal deletions and tumor suppressor genes in prostate cancer. Cancer Metastasis Rev 2001;20:173-93.
7. Berns EM, Foekens JA, van Staveren IL, van Putten WL, de Koning HY, Portengen H, *et al*. Oncogene amplification and prognosis in breast cancer: Relationship with systemic treatment. Gene 1995;159:11-8.
8. Ross JS, Fletcher JA, Bloom KJ, Linette GP, Stec J, Symmans WF, *et al*. Targeted therapy in breast cancer: The HER-2/neu gene and protein. Mol Cell Proteomics 2004;3:379-98.
9. Chial H. Proto-Oncogenes to Oncogenes to Cancer; 2008. Available from: http://www.nature.com/scitable/topicpage/proto-oncogenes-to-oncogenes-to-cancer-883. [Last accessed on 2021 Jul 05].
10. Bhise SB, Nalawade AD, Wadhawa H. Role of protein tyrosine kinase inhibitors in cancer therapeutics. Indian J Biochem Biophys 2004;41:273-80.
11. Kurzrock R, Kantarjian HM, Druker BJ, Talpaz M. Philadelphia chromosome-positive leukemias: From basic mechanisms to molecular therapeutics. Ann Intern Med 2003;138:819-30.
12. Li Y, Roberts ND, Wala JA, Shapira O, Schumacher SE, Kumar K, *et al*. 356 patterns of somatic structural variation in human cancer genomes. Nature 2020;357:112-21.
13. Mitelman F, Johansson B, Mertens F. The impact of translocations and gene fusions on cancer causation. Nat Rev Cancer 2007;7:233-45.
14. Pon JR, Marra MA. Driver and passenger mutations in cancer. Annu Rev Pathol 2015;10:25-50.
15. Gillies RJ, Gatenby RA. Hypoxia and adaptive landscapes in the evolution of carcinogenesis. Cancer Metastasis Rev 2007;26:311-7.
16. Gatenby RA, Gillies RJ. Why do cancers have high aerobic glycolysis? Nat Rev Cancer 2004;4:891-9.
17. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100:57-70.
18. Holmgren L, O'Reilly MS, Folkman J. Dormancy of micrometastases: Balance proliferation and apoptosis in the presence of angiogenesis suppression. Nat Med 1995;1:149-53.
19. Parangi S, O'Reilly M, Christofori G, Holmgren L, Grosfeld J, Folkman J, *et al*. Antiangiogenic therapy of transgenic mice impairs de novo tumor growth. Proc Natl Acad Sci USA 1996;93:2002-7.
20. Rebecca W. Apoptosis in cancer: From pathogenesis to treatment. J Exp Clin Cancer Res 2011;30:87.
21. Zahreddine H, Borden KL. Mechanisms and insights into drug resistance in cancer. Front Pharmacol 2013;4:28.
22. Salem H, Attiya G, El-Fishawy N. Classification of human cancer diseases by gene expression profiles. Appl Soft Comput 2017;50:124-34.
23. Nowell PC, Hungerford DA. National academy of sciences. Science 1960;132:1488-501.
24. Rowley JD. A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and giemsa staining. Nature 1973;243:290-3.
25. Hehlmann R, Hochhaus A, Baccarani M. Chronic myeloid leukaemia. Lancet 2007;370:342-50.
26. Roy PG, Thompson AM. Cyclin D1 and breast cancer. Breast 2006;15:718-27.
27. Peto J, Collins N, Barfoot R, Seal S, Warren W, Rahman N, *et al*. Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer. J Natl Cancer Inst 1999;91:943-9.
28. Bogaert J, Prenen H. Molecular genetics of colorectal cancer. Ann Gastroenterol 2014;27:9-14.
29. Vogelstein B, Lane D, Levine AJ. Surfing the p53 network. Nature 2000;408:307-10.
30. Andreyev HJ, Norman AR, Cunningham D, Oates J, Dix BR, Iacopetta BJ, *et al*. Kirsten ras mutations in patients with colorectal cancer: The "RASCAL II" study. Br J Cancer 2001;85:692-6.

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