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Genetic Causes of Cancer:

Background

Cancer cells (malignant cells) break two rules imposed on all cells in a multicellular organism: they and their progeny do not adhere to restrained cell division, and they invade and colonize tissues reserved for other cell types. A cancer is medically classified according to the cell type from which it originates:

Carcinoma from epithelial cells,

Sarcoma from connective tissue and muscle cells,

Leukemia from hematopoietic cells, and

Lymphoma from lymphoid cells.

Genetically, cancer is either non hereditary, due to somatic mutations, or hereditary, due to a predisposing mutation in the germline.

Oncogenetics

Although the process and causes of carcinogenesis have already been discussed in several other subjects, this section will cover the major genetic events of the development of tumors, because at cellular level tumors may also be considered genetic disorders. The cancers affect 1 in 3 people worldwide; a man has ~ 40% chance of the cancer. Even this high frequency indicates that tumors are usually not of monogenic origin, with the exception of rare monogenic tumors such as retinoblastoma, or Li-Fraumeni syndrome. There are a number of underlying genetic susceptibility factors (mutations) and environmental effects. The cancer can be described as a group of diseases characterized by unlimited proliferation and spread of mutant cells in the body.

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The following steps are the hallmarks of carcinogenesis:

A. Growth signal autonomy
B. Unlimited replicative potential
C. Evasion of growth inhibitory signals
D. Evasion of apoptosis
E. Angiogenesis
F. Invasion and metastasis

Four basic types of genetic alteration in tumor cells

The many genetic alterations affecting growth controlling genes can be classified into four major categories:

(i) change in the DNA sequence of a growth-controlling gene (somatic mutation),
(ii) reciprocal chromosome translocation disrupting a gene expressed in a tissue that depends on controlled cell division (e.g., immune system, blood cell formation in bone marrow),
(iii) gross alteration in chromosome number in somatic cells during tumor progression, and
(iv) amplification of a growth controlling gene.

Here are four examples.

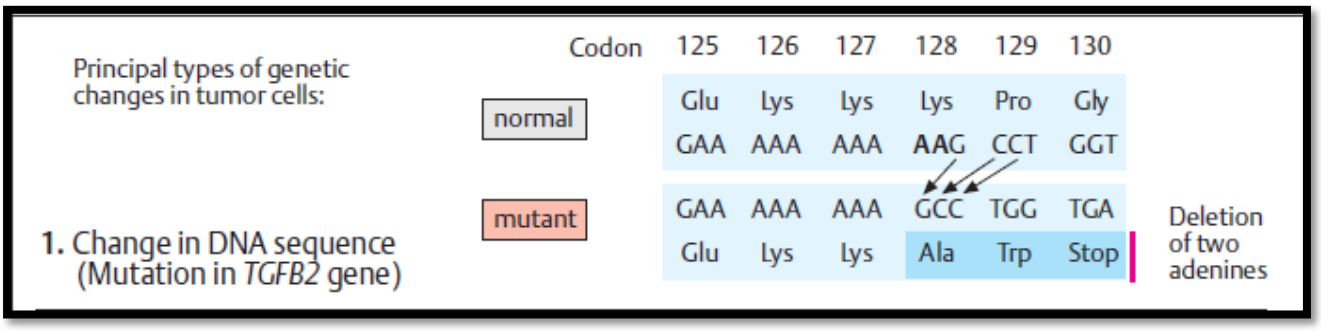
(**1**) ***Change in DNA sequence***. A deletion of two adenines (A) in a series of ten in the gene *TGFBR2* for receptor type 2 of the transforming growth factor beta (TGF_ R2) in a colorectal cancer cell line changes the codon AAG (lysine) to GCC (alanine). This converts the subsequent codons into TGG (tryptophan) and TGA (stop codon), resulting in a truncated protein.

(**2**) ***Chromosome translocation***. A reciprocal translocation between a chromosome 1 and a chromosome 17 in a neuroblastoma (MIM 256700) cell line disrupts genes involved in neuroblastoma located on chromosomes 1 and 17.

(**3**) ***Gross chromosomal change***. Loss of a chromosome 3 and a chromosome 12 (yellow arrows) occurred in a clone of a cell line (SW837) of colorectal cancer cells (CRCs). Such gross changes are frequent during tumor progression.

(**4**) ***Gene amplification***. In some tumor cells in culture, small chromosomal derivatives (double minutes) or homogeneously stained regions (HSRs) are visible. HSRs, first described by Biedler & Spengler (1976), are cytological manifestations of gene amplification. Specific DNA sequences are replicated to a disproportionately higher

degree than normal. Here a metaphase from a clone of the CRC cell line SW837 expanded through 25 generations is shown.



Cancer and genetic

A- Categories of Cancer Gene

Tumors and cancer are the result of uncontrolled cell division. Normally, cell division is regulated by a family of extracellular growth factors, proteins that cause resting cells to divide and, in some cases, differentiate. Defects in the synthesis, regulation, or recognition of growth factors can lead to cancer. Cancer is a common genetic disease that affects 1 of every 4 individuals. **More than 100 genes in the human genome contribute to cancer when altered by mutations.** They are classified into three basic categories according to the effects of their mutations: too much activity of a gene product (**oncogenes**) Their mutant forms, called *oncogenes*, drive a cell to divide when it normally should not (gain-of-function mutations). A single activating mutation is the first step towards cancer , insufficient activity (***tumor suppressor* genes**) They require two mutational events to induce tumor development (comparable to a defective brake). The initial mutation predisposes the cell to become a cancer cell. The second mutation then inactivates the other allele (loss-of-function mutation) and results in loss of cell division control. , and **disruption of *genome stability* genes,** Mutations in the third class of cancer genes, called *stability genes* or *caretakers*, affect the stability of the genome by disrupting one of the various repair processes.

B- Oncogene activation

Oncogene were originally discovered in tumor-causing viruses, then later found to be closely similar to or derived from genes in the animal host cells, proto-oncogenes, which encode growth-regulating proteins. During viral infections, the DNA sequence of a proto-oncogene is sometimes copied by the virus and incorporated into its genome.

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Proto-oncogenes can become oncogenes without a viral intermediary. The genetic mechanisms that activate oncogenes include point mutations, chromosome rearrangement (chromosomal translocation), and gene amplification. chemical agents, and radiation are among the factors that can cause oncogenic mutations. The mutations that produce oncogenes are genetically dominant; if either of a pair of chromosomes contains a defective gene, that gene product sends the signal "divide" and a tumor will result.

Oncogenes serve in signal pathways controlling cell division. For example the *Ras* genes encode a family of related cell growth-controlling proteins. Ras proteins are GTPase-binding proteins functioning as switches, inactive when bound to GDP (guanosyldiphosphate) and active when bound to GTP (guanosyltriphosphate). Ras is activated by a receptor tyrosine kinase, which activates a guanine nucleotide exchange factor (GEF). GTPase-activating proteins (GAPs) increase the hydrolysis of GTP bound to Ras and inactivate Ras by removing GTP. Mutant forms of Ras are hyperactive and do not respond to GAPs. Instead they remain bound to GTP, sending continuous cell division-promoting signals to the nucleus through several pathways and causing uncontrolled cell divisions.

C. Tumor suppressor genes

Two successive mutational events are required within the same cell

(1) The first event inactivates one allele and predisposes the cell to uncontrolled divisions. If the other allele is also inactivated by a mutation, cell division control is lost and a tumor develops. One of several mechanisms may be responsible: a further mutation, chromosome loss during cell division (mitotic nondisjunction), or mitotic recombination with gene conversion. Tumor suppressor genes can be assigned to two groups, ***gatekeepers*** and ***caretaker***s. ***Gatekeeper* genes *directly*** inhibit tumor growth. Inactivation **of caretaker genes** leads to genetic instability, indirectly promoting tumor growth. Loss of one allele in a somatic cell carrying a mutation in the other allele.

(2) Whereas somatic cells heterozygous at a marker locus give two signals, tumor cells, which have lost both alleles of the gene, give one signal (loss of heterozygosity, LOH). LOH is a hallmark of a tumor suppressor gene. It occurs with variable frequency in different tumors and may be useful in detecting a mutation indirectly. Mutations in tumor suppressor genes may be present in the zygote (by transmission or by new mutation) or occur in a somatic cell (**3**). A germline mutation predisposes

all cells to develop into tumor cells. A somatic mutation predisposes a single cell. Germline mutations are the basis for hereditary forms of cancer; somatic mutations for the nonhereditary forms. A germline mutation occurring after the initial division of the fertilized egg may result in amosaic of mutated and normal cells.