Tumor Supressor Genes

A tumor supressor gene is a gene that prevents a cell from developing into a cancer cell. Unlike oncogenes, both alleles that code for a particular protein must be affected before an affect is manifested. Therefore, mutations in these genes contribute to malignancy through loss of function of both alleles of the gene. This is called the two-hit origin of cancer The two-hit theory explains inherited predisposition to cancer diseases, such as retinoblastoma or Li-Fraumeni syndrome. In these cases, cancer might be initiated when a cell in a person heterozygous for a germline mutation in a tumor-suppressor gene, undergoes a second, somatic event that inactivates the other allele. As a consequence, the cell loses function of both alleles, giving rise to a tumor. Second-hit may also be due to epigenetic factors ! (silencing the gene). If the two mutations are sporadic form of a cancer, both alleles are also inactivated but from two somatic events occurring in the same cell.

Caretakers

Caretakers are genes that protect the integrity of the genome. They are also called mutator genes because once they are mutated, the rate of mutations increases. These genes are either directly or indirectly responsible for repair of DNA. However, the distinction between caretakers and gatekeepers is not always clear and cut. For example, tp53 is usually classified as a gatekeeper because it regulates the cell cycle and therefore the proliferation of the cell. But tp53 does also have a caretakers function because it stops the cell cycle and gives the repair proteins time to fix the damaged DNA, therefore protecting the integrity of the genome.

Caretakers do not directly influence cell proliferation but are still very important in the prevention of cancer because without them, the mutation rate would be a lot higher and that would lead mutations of gatekeepers and oncogenes. Therefore, caretakers in a way act as a first line of defense against cancer. These genes are of several types, depending on the mechanism by which they act. Each type is responsible for hereditary predisposition of cancer once the functional gene is lost. For example:

- DNA mismatch repair is a mechanism where the template strand is distinguished from the lagging strand and the repair proteins are therefore able to review the action of the DNA polymerase after replication. Defects lead to Hereditary Nonpolyposis Colorectal Cancer.
- Nucleotide excision repair is a mechanism which removes a faulty nucleotide and few adjacent nucleotides before DNA polymerase and DNA ligase repair the broken strand. If it's defected it leads to the rare disorder Xerdoerma Pigmentosum (XP). A person with XP will have high mutation rate from UV light and can develop multiple basal cell carcinomas and other skin malignancies.

Gatekeepers

Gatekeepers are proteins that directly control the cell cycle. As apposed to caretakers genes that indirectly lead to cancer by allowing accumulation of mutations, a mutation in a gatekeeper (of both its alleles) will directly lead to cancer by allowing uncontrolled cell growth. They indirectly prevent mutations by halting the cell cycle if DNA is damaged, stimulating its repairation.

Examples of their functions

- Inhibit S phase
- Inhibit action of mitogen
- Activate genes that produce proteins that inhibit proliferation

Examples of gatekeepers

p53

If DNA is damaged p53 will halt the cell cycle before S phase in G1. It does this by upregulating p21. P21 will bind to the cyclin-cdk complexes needed to enter S phase inactivating them. If the DNA is too severely damaged p53 will lead the cell into apoptosis

Retinoblastoma Protein – Rb

Inhibits transcription of proteins needed to enter S-phase by binding to them. It will be released from these proteins by the products of an enzyme cascade resulting from the interaction of a mitogen with a receptor. In the absence of such a signal the cell will slip into a phase quiescence called G0. Adenomatous polyposis coli – APC. This protein is part of the the Wnt singnalling pathway. Upon the interaction of a Wnt, an extracellular signalling molecule, with its receptor, frizzled, a bunch of other downstream proteins are activated. This results in the activation of APC. APC works to degrade cytoplasmic beta-catenins. Cytoplascmic beta-catenins would otherwise be able to activate cellular proliferation genes, such as the transcription factor Myc.

Links

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