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Author
Campisi, Judith

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Genetics: Tumor Suppression

Long-lived organisms have had to evolve mechanisms to suppress the development of cancer. These mechanisms are termed tumor suppression mechanisms, and the genes that control them are termed tumor suppressor genes. Tumor suppressor genes promote the development of cancer when they are lost or inactivated.

Many genes have been shown to function as tumor suppressors. Most participate in normal cellular and developmental processes, where the proteins they encode act to inhibit cell proliferation or promote differentiation or apoptosis. Tumor suppressors also play important regulatory and functional roles in the sensing and repairing of DNA damage, and the response to DNA damage, namely cellular senescence and apoptosis.

Proteins encoded by tumor suppressor genes include growth inhibitory cytokines and their receptors, such as some members of the TGF-β (transforming growth factor-beta) family and their transmembrane receptors. They also include transmembrane proteins such as E-cadherin, which organizes cells in epithelial tissues and promotes their differentiation. Some nuclear receptors, such as some of those that bind retinoic acid (RARs or retinoic acid receptors), can also act as tumor suppressors. In addition, proteins that transduce growth inhibitory signals, such as those that transduce TGF-β and related signals, as well as transcriptional regulators that respond to growth inhibitory signals, such as the retinoblastoma susceptibility protein (pRB), can be tumor suppressors. Pro-apoptotic proteins comprise another class of tumor suppressors -- for example BAX, which stimulates opening of the mitochondrial permeability pore, a prelude to apoptosis. Finally. proteins that sense or regulate the repair of DNA damage, or control the cellular response to DNA damage, can be tumor suppressors. Example include ATM (ataxia

telangiectasia mutated), a protein kinase that transduces damage signals to p53, and p53 itself, a transcription factor that induces either cellular senescence, apoptosis, or cell cycle arrest and DNA repair.

Loss or inactivation of tumor suppressor genes can occur by genetic (necessarily hereditary) or epigenetic (not necessarily hereditary) mechanisms. Genetic mechanisms include deleterious mutations or deletion of all or part of the gene. Epigenetic mechanisms include gene silencing, as well as any change in synthesis, degradation, localization or interaction that prevents the gene product from functioning. Because cancer phenotypes generally result from loss of tumor suppressor gene functions, oncogenic mutations in these genes tend to recessive -- that is, both gene copies must be inactivated before cell behavior is affected.

Because many tumor suppressors function in normal cellular and developmental processes, they tend to be key participants in pathways that control cell growth, death, differentiation and/or repair.

Two of the most important tumor suppressor pathways are those controlled by the *RB* and *TP53* genes, which encode the pRB and p53 proteins, respectively. Most, if not all, cancers harbor mutations in either the pRB or p53 pathway, or both.

pRB and p53 regulate the transcription of other genes. pRB does so indirectly by binding and regulating transcription factors or transcription modulators. pRB inhibits cell cycle progression, largely by repressing the activity of E2F, a transcription factor that induces the expression of genes needed for DNA replication. p53, by contrast, is a direct transcription factor that induces the expression of cell cycle inhibitors in response to DNA damage. Consistent with their key roles in tumor suppressor pathways, pRB and p53 are controlled by upstream regulators

and their activities are mediated by downstream effectors. Examples of upstream regulators are p16, which inhibits the cyclin-dependent protein kinase that phosphorylates and inactivates pRB, and ATM, which phosphorylates and activates p53. Examples of downstream mediators are E2F, the transcription factor that is blocked by pRB, and p21, the cyclin-dependent kinase inhibitor whose transcription is induced by p53.

Oncogenic mutations in pRB tend to be deletions, typical for tumor suppressor genes. By contrast, although some p53 mutations are deletions, many cancer cells harbor point mutations in p53. These point mutations alter its functions as a transcription factor, and are dominant.

Tumor suppressor genes are generally identified by their ability to increase the incidence of cancer when one or both copies are defective in the germline, and by their consistent absence in malignant tumors.

Germline tumor suppressor gene mutations are rare, and generally heterozygous (only one allele is mutant). This is because, although homozygous mutations favor the growth and/or survival of cancer cells, they are often lethal during embryogenesis. For example, mice lacking both *RB* genes do not survive to birth, whereas mice carrying one mutant and one wild-type *RB* allele develop normally but die of cancer at an early age. The tumors invariably show loss of the wild-type allele, indicating that once development is complete, loss of pRB results in cancer. This is also true in humans -- children with one defective and one normal *RB* allele are normal at birth. However, they have a high incidence of childhood retinoblastoma and other tumors, and the tumors inevitablty have lost the wild-type allele.

Most cancers, of course, develop in organisms with a genetically normal germ line. Nonetheless, tumors generally harbor loss or inactivation of both copies of tumor suppressor

genes. One reason why most cancers develop relatively late in life is that it takes time for mutations to develop in both tumor suppressor genes within a single cell.

Not all tumor suppressor genes are critical for normal development. Rather, some tumor suppressors appear to act primarily to suppress the development of cancer during adulthood. For example, genetically engineered mice that completely lack p16 develop normally, but die of cancer during young adulthood. Similarly, mice completely deficient in p53 develop normally, but develop cancer at an early age. When only one p16 or p53 gene is deleted, cancer incidence is lower than in animals that lack both genes, but higher than in wild type animals. Tumors that develop in these animals invariably lose the remaining gene or, in the case of p53, acquire a dominant mutation in it. Tumor suppressor genes of this type, then, appear to act as longevity assurance genes. That is, they act to prevent the development of cancer during young adulthood or the peak of reproductive fitness. It is not surprising that tumor suppressors of this type also tend to be critical regulators of apoptosis and/or cellular senescence. Cellular senescence and apoptosis are potent tumor suppressive mechanisms in mammals that also appear to play important role in the development of aging phenotypes.

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