BNB

ACTIVATION OF PROTO-ONCOGENES

Most human and other animal oncogenes are mutant forms of normal cellular genes. Such genes in their normal state are called Proto-oncogenes. Proto-oncogenes are normal cellular genes that make essential contributions to the regulation of cell growth and survival and also differentiation. When Proto-oncogenes become mutated or translocated such that they induce tumor formation, they are called Oncogenes (from the Greek Oncos = "tumor").

Proto-oncogenes are activated to oncogenes by various mechanisms such as:-

1. Point mutations (base pair substitutions):-

Point mutations in the coding region of a gene or in the controlling sequences (promoters, regulatory elements, & enhancers) can change a proto-oncogene into an oncogene by causing an increase in either the activity of the gene product or the expression of the gene leading in turn to an increase in the amount of gene product.

For example, the ras genes are a family of genes encoding membrane associated G proteins. A single point mutation, generally in codons 12, 13 or 61, results in a mutant protein that can transform normal cells into malignant cells. These types of mutations are found in malignant cells from patients with bladder cancer, lung cancer, colon cancer and leukemia. The effect of the mutation is to cause the G-proteins to lose their ability to be regulated so that constitutive growth signals (growth signals that always being produced) are transmitted into the cell. As a result, unregulated cell proliferation can commence.

2. Gene Amplification (increased number of copies of the gene):- Some tumors have multiple copies of Proto-oncogenes (sometimes hundreds). These probably result from a random over-replication of small segments of

the genomic DNA. In general, ~~proto~~ extra copies of the proto-oncogene, in the cell result in an increased amount of gene product, thereby inducing or contributing to unscheduled cell proliferation. For example, multiple copies of ras are found in mouse adrenocortical tumors.

Moreover, about 25% of human breast and ovarian cancers have amplified copies of the ERBB2 gene, which codes for a growth factor receptor. The existence of multiple copies of the gene leads to the production of too much receptor protein, which in turn causes excessive cell proliferation.

3) Deletions:- Deletion of parts of the coding region or parts of the controlling sequences of a proto-oncogene has been found frequently in oncogenes. The deletions cause changes in the amount or activity of the encoded growth stimulating protein, causing unprogrammed activation of some cell proliferation genes.

For example, the myc oncogene can arise from its proto-oncogene by deletion. The normal gene consists of 3 exons & 2 introns; in some commonly found myc oncogenes the first exon and most of the first intron are deleted. Transcription is then controlled from sequences in exon 2, which can function as a promoter. The myc proto-oncogene encodes a nuclear transcription factor that positively regulates the genes involved in cell proli-feration. Thus, the deletions in the oncogene forms have brought about a change in the amount or activity of the remaining myc protein chain that activates those genes.

4) Insertional mutagenesis:- Retroviruses are common causes of cancer in animals, although only one type of cancer is known for humans. A retrovirus can cause cancer if it is a transducing retrovirus and V-onc, it carries, is expressed. In this case,

transcription of the v-onc takes place under the control of retroviral promoters. Another way in which a retrovirus can cause cancer is the integration of the provirsal DNA near a proto-oncogene. In this situation, expression of the proto-oncogene can come under control of retroviral promoter and enhancer sequences in the terminal LTR (Long Terminal Repeat). These retroviral sequences do not respond to the environmental signals that normally regulate proto-oncogene expression; so ~~over exp~~ over-expression of the proto-oncogene occurs transforming the cell to the tumorous state. The process of proto-oncogene activation is called **Insertional mutagenesis.**

5) Chromosomal Rearrangements:-

(A) Philadelphia chromosome:- Certain types of human cancer are associated with chromosome rearrangements. For example, Chronic Myelogenous Leukemia (CML) is associated with an aberration of chromosome 22. This abnormal chromosome was originally discovered in the city of Philadelphia and thus is called as Philadelphia chromosome (Ph¹).

Initially, it was thought to have a simple deletion in its long arm; however, subsequent analysis using molecular techniques have shown that the philadelphia chromosome is actually the result of a reciprocal translocation between chromosomes 9 and 22. In the Philadelphia translocation, the tip of the long arm of chromosome 9 has been joined to the body of chromosome 22, and the distal portion of the long arm of chromosome 22 has been joined to the body of chromosome 9.

The translocation breakpoint on chromo-some 9 is in the c-abl oncogene, which encodes a tyrosine kinase, and the breakpoint on chromosome 22 is in a gene called bcr. Through translocation, the bcr & c-abl

genes have been physically joined, creating a fusion gene whose polypeptide product has the amino terminus of the Bcr protein and the carboxy terminus of the Abl protein.

Mechanism:- Although it is not understood precisely why, this fusion polypeptide causes ~~its~~ WBCs to become cancerous. The mechanism may involve the tyrosine kinase activity of the C-Abl protein, which is tightly controlled in normal cells but is deregulated in cells that produce the fusion polypeptide. In effect, the tyrosine kinase function of the C-Abl protein has been constitutively activated by the bcr/c-abl gene fusion. This fusion is therefore a dominant activator of the C-Abl tyrosine kinase. Deregulation of the c-Abl tyrosine kinase leads to abnormal phosphorylation of other proteins, including some that are involved in controlling the cell cycle. In their phosphorylated state, these proteins cause cells to grow & divide uncontrollably.

(B) Burkitt's Lymphoma:- Burkitt's Lymphoma is another example of a WBC cancer associated with reciprocal translocation. These translocations invariably involve chromosome 8 and one of the three chromosomes (2, 14, and 22) that convey genes encoding the polypeptides that form immunoglobulins. Translocations involving chromosomes 8 and 14 are the most common. In these translocations, the c-myc oncogene on chromosome 8 is juxtaposed to the genes for the Immunoglobulin Heavy chains (IGH) on chromosome 14. This rearrangement results in the overexpression of the c-myc oncogene in cells that produce immunoglobulin heavy chains — that is, in the B cells of the immune system. The c-myc gene encodes a transcription factor that activates genes involved in promoting cell division.

consequently, the overexpression of c-myc that occurs in cells that carry the IGH/c-myc fusion created by the t8;14 translocation causes those cells to become cancerous.