Proto-oncogenes, oncogenes

A group of genes (but also miRNAs) whose products are mainly stimulants of cell division, inhibitors of cell differentiation, or signals for prolonged cell life. **Proto-oncogene** changes to oncogene mainly by somatic point mutations, gene amplifications, or chromosomal translocations that bring proto-oncogene under control of differentially expressed protein. **Oncogenes** have a strong potential to lead the cells into cancer. Mutations of one allele are responsible for oncogenic potential; they have a **dominant effect**. Disturbing the function or the level of such specific protein in the cell environment is sufficient to cause overstimulation of the cell division, stopping of the cell differentiation and immortality.

Typical products of proto-oncogenes are signaling molecules, growth factors or growth factor receptors. Aberrant expression of oncogene acts on different levels:

1. It is present in a cell where it previously was absent
2. It is in an appropriate cell but in a changed amount (usually excessive amount)
3. Its protein structure is changed to an extent that it cannot be regulated by normal mechanism

Examples

- **Her2** (or ERBB2) (Human epidermal growth factor receptor 2) – **tyrosin-kinase receptor** protein, expressed on the breast cells controls the extent of growth. About 25% of breast cancer patients show overexpression of HER2 receptor caused mainly by HER2 gene amplification.
- **KRAS** – (Kirsten rat sarcoma viral oncogene homolog) – One of many RAS proteins. It is a **GTPase** involved in signal transduction pathway in many cells. KRAS binds to GTP in its active form and once it cleaves the terminal phosphate of the nucleotide it releases GDP and becomes inactive. Interestingly, there are common sites of KRAS gene somatic mutations (mainly changing guanine to other nucleotides) which make the oncoprotein to provide excessive growth promoting signal. About 50% of colorectal tumors show mutated KRAS gene.
- **c-jun** - This gene is the putative transforming gene of avian sarcoma virus 17. It encodes a **transctiption factor** and its structure is highly similar to the viral protein. It interacts directly with specific DNA sequences to regulate expression of target genes. Jun gene maps to chromosomal region 1p32-p31, involved in both translocations and deletions in human malignancies. C-Jun is overexpressed in about 30% of Non-small cell lung cancers.

Many oncogenes derived from cellular proto-oncogenes have been found in different retroviruses, implying that the normal vertebrate genome contains many potential cancer-causing genes. Oncogenes were primarily identified in viruses causing cancers in chicken (1911, by Peyton Rous). Today we are aware of many oncoviruses that are responsible for causing cancer in humans: adenoviruses (lung cancers), papoviruses (cervix cancer), retroviruses (leukemias) and herpesviruses (Burkitt lymphoma). In humans, we know over 40 proto-oncogenes. Oncogenes are product of interaction between organisms and environment and cannot be inherited as syndromes known in tumor suppressor genes defects.