

causation because a nonspecific viral like illness characterized by fever, malaise, leukocytosis, respiratory symptoms etc. Viral infection may also decrease the immunologic capability of the individual to protect against cancer.

10.1.4 Hormones and carcinogenesis

Hormones are supposed to be carcinogenic agents, especially when elevated.

Estrogens may be responsible for development of breast cancer and endometrial cancer. Some malignant cells of breast cancer appear to have estrogen hormone receptors that allow binding to hormone molecules to take place, which then causes cellular division and growth. Also endometrial cancer may be associated with estrogen replacement therapy.

Diethylstilbestrol administered to prevent abortion has been linked to an increased incidence of vaginal and testicular cancer in children of women with such treatment in pregnancy.

Elevated levels of hormones may act as promoters by increasing of normal cellular proliferation or they may promote also tumor growth and dissemination.

10.1.5 Irritation and carcinogenesis

Irritation may also play a role in carcinogenesis. Continuous irritation of skin or mucose may promote malignancy. It is well known that irritation support development of malignant melanoma from a previously benign pigmented mole. Also using intrauterine devices may subject uterus to prolonged irritation and may increase risk of development of cancer. Some components of smoke and alcohol may promote carcinogenesis acting as irritating factors.

ral oncogene (e.g. c-src, c-myc, c-myb etc). They are not cancer genes. The term "proto-oncogenes" is used to denote their ability to require an oncogenic potential.

In normal cells they have functions in cell growth and differentiation: They

- code for phosphorylate proteins
- influence DNA replication
- control mRNA production
- bind GTP

Since the retroviral oncogenes are mutants of normal proto-oncogenes, they have provided a key to open a door to understand proto-oncogene – oncogene conversion. It was accepted that following crucial events may be responsible for conversion of proto-oncogenes to "cancer" genes:

- **mutations** (point mutations of proto-oncogenes or their regulatory genes caused by chemicals, radiation, viruses)
- **amplifications**
- **translocations** (proto-oncogene is placed in proximity to a strong promoter)

An example is found in Burkitt's lymphoma, where the translocation of c-myc proto-oncogene from chromosome 8 to chromosome 14 is often observed. In this instance, the oncogene c-myc of chromosome 8 becomes activated when is transcribed in tandem with either heavy chain genes (IgH genes) of chromosome 14 or with immunoglobulin light chain genes of chromosomes 2 and 22.

Altered c-myc play an important role in B cell tumorigenesis. Normal proto-oncogene c-myc is expressed in normal proliferating lymphoid cells and presumably this expression is a signal for continued growth. In terminally differentiating B cells, c-myc transcription is arrested, resulting in a non-proliferating plasma cell. However, when chromosomal rearrangements bring c-myc into the proximity of an immunoglobulin gene locus, c-myc transcription can be positively driven by that locus, thus providing continued proliferation to plasma cell.

Another example is the translocation 9, 22 in 90% patients with chronic myelogenous leukemia, where the proto-oncogene c-abl from chromosome 9

10.2 Cellular oncogenes

Mammalian cells possess a set of normal cellular genes – proto-oncogenes (c-onc) and tumor suppressor genes.

Proto-oncogenes are termed also as cellular oncogenes (c-onc) with acronym from corresponding vi-

is translocated to the abbreviated chromosome 22 known as the Philadelphia chromosome (Ph^1). In this disorder an abnormal transcription of *c-abl* has been found.

Detection of chromosomal abnormalities using high resolution chromosome techniques are very important for diagnosis and prognosis. On the basis of such detection acute nonlymphocytic leukaemia can be subdivided into 17 categories with prognosis varying from poor to long survival. **Chromosomal abnormalities** predisposing to cancer are **inherited or acquired** (Tab. 10.1 and Tab. 10.2).

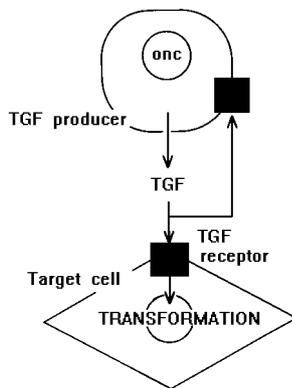


Figure 10.3: Production and action of transforming growth factors (TGFs)

Mutated, inappropriately amplified or translocated proto-oncogenes may encode for

1. excessive, unregulated quantity or
2. chemically altered quality of gene products.

Of particular interest in neoplastic transformation is a role of such gene products as polypeptide growth factors and their receptors. The growth factors implicated are the platelet-derived growth factor (PDGF) and epidermal growth factor (EGF). Polypeptide growth factors potently stimulate normal cellular proliferation. The interaction of growth factors with their specific receptor starts a cascade of

morphological and biochemical events which can result in the proliferative response. For example *c-sis* proto-oncogene encodes for PDGF, which participates in a normal repairing process by stimulating growth of fibroblasts and by influencing of platelet aggregation. If proto-oncogene *c-sis* is altered, it may code for a polypeptide similar in function to PDGF – PDGF like transforming factor, which is able to disrupt normal cell proliferation (Fig. 10.3). Proto-oncogene *c-erb* encodes another polypeptide epidermal growth factor receptor. Altered *c-erb* may code for truncated form of EGF receptor which may be responsible for generating an uncontrolled proliferative signal. Altered *c-erb* is associated with squamous cell cancer and glioblastoma.

Many of the normal proto-oncogene products have a tyrosine kinase activity. This activity leads to self-phosphorylation and phosphorylation of other proteins. Tyrosine phosphorylation is an important mediator of growth regulatory mechanisms and morphological cell phenotype.

Product of another proto-oncogene exhibits GTPase activity.

Alteration of one proto-oncogene is not sufficient for development of malignancy, but a cascade of sequential proto-oncogene alterations may be necessary.

10.3 Characteristics of cancer cells

The cancer cells show **cellular and nuclear pleomorphism**, they **loss of normal arrangement of cells**, they develop **changes in the cell membranes and organelles** (Fig. 10.4), they exhibit **abnormal mitoses and chromosomal abnormalities**.

Increased **motility** of malignant cells may be associated with increased amounts of contractile proteins in their microfilaments, with loss of contact inhibition (probably caused by alteration in calcium ion concentration in the malignant cell membrane).

Interrupted cellular adhesiveness (for the solid surface) and **contact inhibition** (among cells) may result from changes in the cell surface glycoproteins