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).

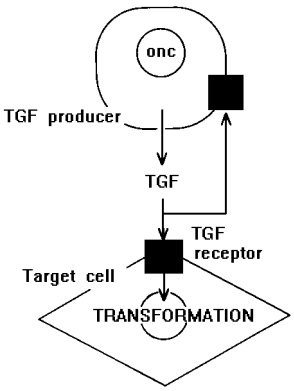

Figure 10.3: Production and action of transforming growth factors (TGFs)

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). Polypetide 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 polypetide 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 squamose cell cancer and glioblastoma.

Many of the normal proto-oncogene products have a tyrosine kinase activity. This activity leads to self-posphorylation 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 develope **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

Inherited chromosomal abnormalities	*Tumor type*
Down's syndrome (trisomy 21)	Acute leukaemia
Klinefelter's syndrome (47,XXY)	Breast cancer
Anirida–Wilm's syndrome ($11p^-$)	Wilm's tumor
Mosaicism (45XO,46XY)	Gonadoblastoma
Multiple malformations ($13q^-$)	Retinoblastoma

Table 10.1: Inherited chromosomal abnormalities and malignancy

Acquired chromosomal abnormalities	*Tumor type*
Translocation (8;14)	Burkitt's lymphoma
Translocation (9;22)	Chronic myelogenous leukaemia
Translocation (15;17)	Acute promyelocytic leukaemia
Deletion (5)	Acute nonlymphocytic leukaemia
Deletion (6)	Acute lymphocytic leukaemia

Table 10.2: Acquired chromosomal abnormalities and malignancy

and the poorly developed tight junctions and desmosomes in malignant cells. Changes in motility, adhesiveness and contact inhibition may promote invasion and subsequent establishment of secondary malignant growth – metastasis.

The cancer cells exhibit **differences in metabolism** as compared to normal cells. The metabolism of malignant cells is usually more anaerobic than that of normal non-rapidly dividing cells and is greatly accelerated. Malignant cells may be able to withstand hypoxic conditions. They may have increased glucose and amino acid uptake. These cells have high levels of hexokinase increasing their glucose utilization.

The cancer cells **loss capabilities to synthesize specialized proteins typical for differentiated cells**. Enzymes and other proteins produced by cancer cells are needed for the tumor growth.

The standard characteristics of cancer cells are:

1. loss of regulation of mitotic rate (Fig. 2.5)
2. loss of specialization and differentiation of the cell
3. ability to move from the original site and establish new malignant growth at other tissue sites (metastasis)
4. capacity to invade and destroy normal tissue

10.3.1 Tumor cell markers

The cancer cells have ability to produce some substances – **tumor cell markers** – that are found on tumor cell membranes and in cytoplasm. These substances may be detected in the blood, urine or spinal fluid.

Immunochemical analysis of serum levels of tumor cell markers enabled us:

1. to identify individuals at high risk of cancer
2. to diagnose the specific type tumor

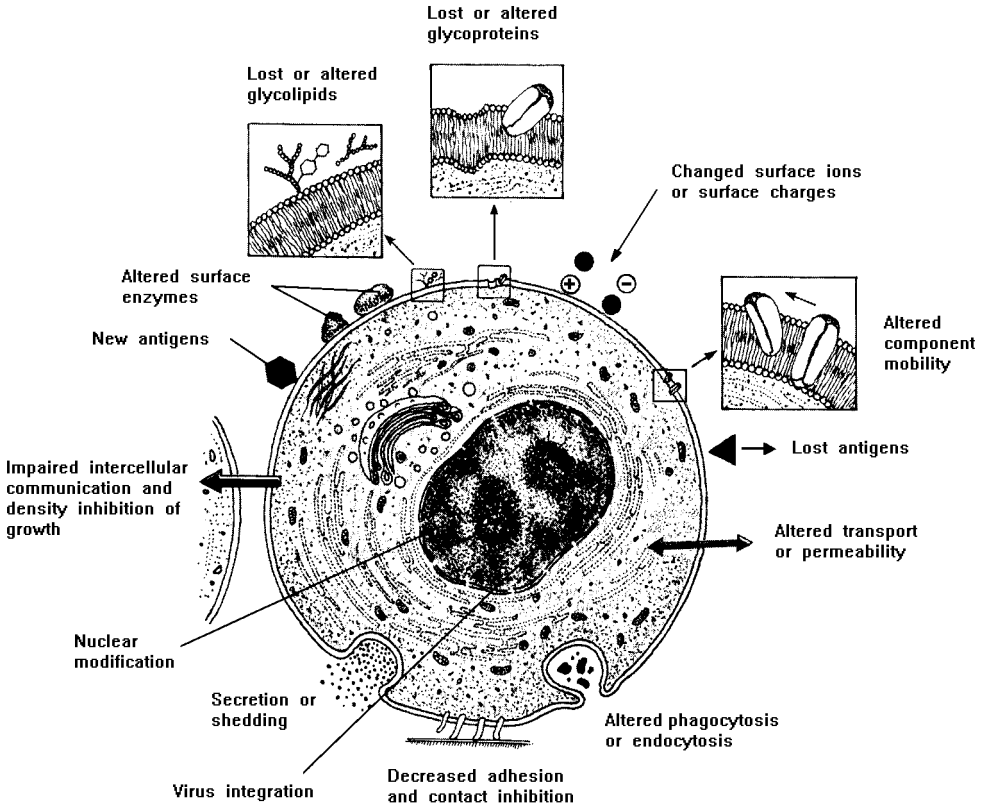

Figure 10.4: Characteristic features of malignant cell (adapted from McCance KL, Mooney KH, Roberts LK: Pathophysiology, 1990)

3. to follow the clinical course of malignant disease

4. to assess effectiveness of therapy

Tumor cell markers include **antigens, enzymes and hormones**. (Tab. 10.3)

Some cancer cells may produce oncofetal antigens, such as alpha-fetoprotein and carcinoembryonic antigen. These proteins are participated in embryogenesis, however in the mature organisms their productions quickly declines after birth. However, titers of antibodies to carcinoembryonic antigen (CEA) are detectable in 90 % patients with cancer of the pancreas, in 70 % patients with cancer of the colon and in 35 % patients with breast cancer. Only approximately 5 % of normal individuals have detectable CEA reactive antibody titers. Increased levels of oncofetal antigens have also been observed in pregnant women, heavy cigarette smokers, patients with acute viral hepatitis etc.

Some tumors inappropriately produce hormones and enzymes. Detection of these tumors occurs through abnormal serum levels of these markers.

10.3.2 Similarity of embryonic and malignant cells

Carcinogenesis may be **a caricature of normal histogenesis** observed in the developing embryo as it differentiates toward a mature organism.

Some characteristics of the cancer cells are reminiscent of the embryonic cells. Cancer cells resemble embryonic cells in motility, decreased con-

Markers	*Tumor type*
Antigens	
Carcinoembryonic antigen (CEA)	adenocarcinomas
Alfa fetoprotein (AFP)	testicular, ovarian, hepatic carcinomas
Tissue peptide antigen (TPA)	carcinomas
Squamous cell carcinoma antigen (SCCA)	epidermoid carcinomas
Antigenic determinants detected by monoclonal antibodies (CA 15-3, CA 125, CA 19-9)	pancreatic, breast, ovarian carcinomas
Hormones	
Human chorionic gonadotropin (HCG)	trofoblastic tumors
Calcitonin (CT)	thyroid, oat cell lung carcinomas
Adrenocorticotrophic hormone (ACTH)	oat cell lung carcinomas
Insulin, gastrin	pancreatic carcinomas
Parathormone (PTH)	oat cell lung carcinomas
Enzymes	
Acid phosphatase	prostatic carcinomas
Alkaline phosphatase	bone tumors
Lactate dehydrogenase	leukaemias
Thymidine kinase	lymphomas, leukaemia
Neuron specific enolase	neuroblastomas, oat cell lung carcinomas

Table 10.3: Tumor cell markers

tact inhibition, invasiveness (which can be compared to the invasive penetration of the endometrium by the trophoblast of the embryo), anaerobic metabolism, anaplasia (loss of differentiation), release of angiogenic (blood vessel-forming) substances, production of embryonic proteins (such as carcinoembryonic antigen).

It has been observed that malignant tumors develop more readily in undifferentiated tissue. These tumors have a higher grade of malignacy. Risk of development of such tumors is associated with prenatal exposure to radiation, stilbestrol therapy, certain viral infections during pregnancy etc.