Cell Transformation and Characteristics of Transformed Cells

Cell transformation and general characteristics of transformed cells.

The four aspects of Cell Transformation are: (1) Genetic Instability (2) Immortalization (3) Aberrant Growth Control and (4) Tumorigenicity.

Cell transformation due to changes in the genetic material, and cell cloning involving the production of a population single cell are described here.

Transformation of Cells:

Transformation broadly refers to the change in phenotype of a cell due to a new genetic material. As regards the cultured cells, transformation involves spontaneous or induced permanent phenotypic alterations as a result of heritable changes in DNA, and consequently gene expression.

Transformation of cells may occur due to any one of the following causes that ultimately result in a changed genetic material:

i. Spontaneous.

ii. Infection with transforming virus.

iii. From gene transfection.

iv. Exposure to chemical carcinogens.

v. Exposure to ionizing radiations.

Characteristics of Transformed Cells:

The general characters of transformed cells are given in Table 39.1. They are grouped as genetic, structural, growth and neoplastic, and listed.

Transormed Cells

Transformation is associated with genetic instability, immortalization, aberrant growth control and malignancy. These aspects are briefly described.

Genetic Instability:

In general, the cell lines in culture are prone to genetic instability. A majority of normal finite cell lines are usually genetically stable while cell lines from other species (e.g. mouse) are genetically unstable,

and can get easily transformed. The continuous cell lines derived from tumors of all species are unstable.

The normally occurring genetic variations in the cultured cells are due to the following causes:

1. High rate of spontaneous mutations in the in vitro conditions, possibly due to high rate of cell proliferation.

2. The continued presence of mutant cells in the culture, as they are not normally eliminated.

Immortalization:

The acquisition of an infinite life span by a cell is referred to as immortalization. Most of the normal cells (from different species) have a finite life span of 20-100 generations. But some cells from mouse, most of the tumor cells have infinite life span, as they go on producing continuous cell lines.

Control of finite life span of cells:

The finite life span of cultured cells is regulated by about 10 senescence genes. These dominantly acting genes synthesize products which inhibit the cell cycle progression. It is strongly believed that immortalization occurs due to inactivation of some of the cell cycle regulatory genes e.g. Rb, p53 genes.

Immortalization of cells by viral genes:

Several viral genes can be used to immortalize cells. Some of these genes are listed below.

SV40LT

HPV16E6/E7

hTRT

Ad5E1a

EBV.

Among the above viral genes, SV40LT is most commonly used to induce immortalization. The product of this gene (T antigen) binds to senescence genes such as Rb and p53. This binding restricts surveillance activity of senescence genes. The result is an increased genomic instability and activity, leading to further mutations favouring immortalization.

For the process of immortalization, the cells are infected with retroviruses containing immortalizing gene before they enter senescence. By this way, the life span of the cells can be extended by 20-30 population doublings. Thereafter, the cells cease to proliferate, and enter a crisis phase that may last for several months. At the end of the crisis phase, a small portion of cells can grow, and eventually become immortalized.

Immortalization of human fibroblasts:

The human fibroblasts are most successfully immortalized by the viral gene namely SV40LT. The process of fibroblast immortalization is complex and indirect with a very low probability i.e. about 1 in 107 cells.

Immortalization of cells by telomerase-induction:

The most important cause of finite life span of cells (i.e. senescence) is due to telomeric shortening, followed by cell death (apoptosis). If the cells are transfected with telomerase gene htrt, the life span of the cells can be extended. And a small proportion of these cells become immortal.

Aberrant Growth Control:

The transformed cells and the cells from tumors, grown in culture show many aberrations with respect to growth and its control. The growth characteristics of these cell are listed in Table 39.1, and some of them briefly described hereunder.

Anchorage independence:

There occur several changes on the cell surfaces of transformed cells. These include alterations in the cell surface glycoproteins and integrin's, and loss of fibronectin. Some of the transformed cells may totally lack cell adhesion molecules (CAMs).

The modifications on the surface of transformed cells leads to a decrease in cell—cell, and cell-substrate adhesion. The net result is that there is a reduced requirement for attachment and spreading of the cells to proliferate. This phenomenon is referred to as anchorage independence. Anchorage independent cells grow in a disorganized fashion. These cells may be comparable with the tumor cells detached from the native tissue which can grow in foreign tissues i.e. formation of metastases.

Contact inhibition:

The transformed cells are characterized by loss of contact inhibition. This can be observed by the morphological changes in the disoriented and disorganized monolayer cells. This results in a reduced density limitation of growth, consequently leading to higher saturation density compared to normal cells.

Low serum requirement:

In general, transformed cells or tumor cells have lower serum dependence than the normal cells. This is mostly due to the secretion of autocrine growth factors by the transformed cells.

Some of the growth factors produced by tumor cells are given:

i. Colony stimulating factor (CSF).

ii. Transforming growth factor (TGFa).

iii. Interleukins 1, 2 and 3.

iv. Vasoactive intestinal peptide (VIP).

v. Gastrin releasing peptide.

It may be noted that many normal cells (fibroblasts, endothelial cells) also produce auto-crine factors during active stage of cell proliferating. Hence, these factors will not be of much use to serve as markers of cell transformation.

Tumorigenicity:

Cell transformation is a complex process that often results in the formation of neoplastic cells. The cell lines obtained from malignant tumors are already transformed.

Such cells may undergo further transformation in the in vitro culture due to:

i. Increased growth rate.

ii. Immortalization.

iii. Reduced anchorage dependence.

For the malignant transformation of cells, several steps may be required.

The following two approaches are in use to understand malignant- associated properties of cultured cells:

1. The cells can be cultured from malignant tumors and characterized.

2. Viral genes or chemical carcinogens can be used to transform the untransformed cells.