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Conceptions about cancer genetics and immortality of cancer cells in 2000

ABSTRACT

Cancer arises as a consequence of the accumulation of mutations in genes controlling cell proliferation, differentiation or death.Thanks to the cancer genetics data,the new definition of cancer is: „cancer is a genetic disease of individual cell - disease of their genes - disease of its cell cycle“ (1). It is a multihit, multistep process. The important steps for malignant transformation are: A. activation of oncogenes, B. inactivation of tumor suppressor genes, C. action of enzyme telomerase on telomeres preventing their shortening, and D. inhibition of apoptosis.The immortality of cancer cell is due to reactivation of enzyme telomerase preventing shortening of telomeres and lack of apoptosis of the cancer cell. Our knowledge about cancer genes and the immortality of cancer cells are the basis for future anticancer therapy by: gene therapy (replacing the wrong genes) or suppressing the wrong genetic informations on the levels of: transcription, translation or executive proteins;suppression of enzyme telomerase; and inducing apoptosis of cancer cells.

KEYWORDS: Neoplasms + genetics; Oncogenes; Telomere; Telomerase; Apoptosis

INTRODUCTION

In spite of some expectations, XXth century did not solve the problem of cancer. Why? Because the world science, specially genetics, molecular biology, gerontology (the causes of senescence), and virology were not developed up to the level to mach the problem of cancer. In 1953 occurs the greatest discovery in genetics and biology: the description of the double helix structure of the genetic molecule deoxyribonucleic acid (DNA) by three scientist: Francis Crick, 1916, biochemist, James D. Watson, 1928, chemist, and Maurice Wilkins, 1916, biochemist (who worked in the field of structural analysis of organic macromolecules using X-ray crystallography).The double - helix model of DNA (Discovered on the bases of the crystalline make-up of DNA) was suitable for explanations of: A. the way in which genetic information is passed on to the „executive organs“ in the cell, and B. how genetic information is reproduced during cell division. For this epoch-making discovery of the structure of DNA, they have been awarded by the Nobel Prize for medicine 1962 (2). In XXth century it was already postulated that „cancer is the disease of the individual somatic cell, probably mutated“.

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GENETICS AND CANCER

Genetics of cancer showed polyploidia of cancer cells with more than two sets of 23 chromosomes and/or abnormal chromosomes (numerical and/or structural anomalies of chromosomes). The karyotypic cancer alterations are common and random. Latter, they were discovered: Philadelphia (Ph 1) chromosome in connection with chronic myelogenous leukemia (chromosome 22 is abbreviated because of reciprocal and balanced translocation between chromosome 22 and 9); deletion of the part of the chromosome 13 (loss of one Rb-1 gene - tumor suppressor gene) in connection with retinoblastoma; and apc gene of the long arm of chromosome 5 in connection with adenomatous polyposis coli.

Protooncogenes and tumor suppressor genes

The crucial thing was the discovery of normal cellular genes: protooncogenes and tumor suppressor genes, as well as their structural mutations, deregulations or loss (1). Protooncogenes exert positive control over cell proliferation and differentiation processes. They encode proteins that function as growth factors or their receptors, and intracellular signal molecules.They are functioning at each step of mitotic cascade. Because of their importance, they are conserved throughout the evolution.

Tumor suppressor genes (anti-oncogenes) exert negative regulatory roles over cellular proliferation. They are inhibiting growth or promoting death. There are two types: A. gatekeepers (prevention of runaway growth), and B. caretakers of the integrity of the genome (encode DNA repair proteins). Inactivation of caretaker genes results in greatly increased rates of mutations and is equivalent to chronic exposure to mutagens. Progression of the normal cell cycle is the result of a balanced interaction among multiple regulators, codified by protooncogenes and tumor suppressor genes. Unbalanced cell cycle leads to eventual cancer progression. Mutation of protooncogene is activating the oncogene. A single mutated copy of a dominant oncogene is enough to trigger cancer. Cellular oncogene (c-onc) is identical to exogenous viral genes(v-onc) carried by oncogenic RNA retro-viruses. C-onc can be isolated and used like viruses to infect normal cells (transfection), transforming them in cancer cells. It can be, also, inserted into mice and studied in vivo, creating transgenic mice which carry foreign (human)genes. Proto-oncogenes can be transformed into oncogenes by: A. Point mutation (substitution of a single base in the DNA chain resulting in a miscoded protein); B. Insertion of the viral genome; C. Chromosomal rearrangements (by translocation or deletion leading to the activation of oncogene); and D. Gene amplification (more copies of oncogene trigger cancer easier).

Inactivation (mutation) of tumor suppressor genes triggers cancer if two their copies are mutated (recessive genetic behavior). There are different tumor suppressor genes: Rb-1, deletion of a segment of the long arm of chromosome 13 (absence in retinoblastoma); apc, on chromosome 5 (absence in familial adenomatous polyposis coli; + secondary mutation of the normal inherited gene on the other allele results in colon carcinoma); p53, on chromosome 17 (lost in many tumors).

p53 protein, encoded by p53 gene, is the best known protein in biology (12500 papers up to 1999!). Its identification is made by D. Lane, 1979, as a cellular protein intimately involved in transformation of cells by the SV 40 virus. For the purpose of comparison, we can use the following cancer - car homology (1): Activation of oncogene would be akin to a jammed gas pedal, and inactivation of tumor suppressor genes would be akin to loss of the brakes. Procancer genes are: oncogenes, genes for dedifferentiation, immortalization, and antiapoptosis.Anticancer genes are: tumor suppressor genes, genes for differentiation, senescence, and proapoptosis (3).

The genetic alterations include mutations, chromosomal translocation and deletions, and gene amplifications causing genetic instability. Inactivation of the tumor suppressor genes p53 and p16 ink 4a or activating mutations in

the ras oncogene are the most common genetic alterations found in human cancer.

Immortality of cancer cell

The number of divisions of normal cell in tissue culture is limited (4). However, the cancer cells taken 1941 from the cervical cancer of patient Helen Lane (the name is fictitious to protect the privacy of patient) - He-La cells do not stop their divisions in tissue culture , i.e.,they are immortal (5,6). These cells are kept in cell culture indefinitely and are used in experimental cancer studies in many laboratories throughout the world. The basis of cancer cells immortality are: A. action of telomerase on telomeres, and B. lack of apoptosis.

A. Telomeres, telomerase and cancer cell

After the cell division, the two normal identical daughter cells grow, differentiate and can achieve limited number of mitoses in the tissue culture (4). After that, they enter into „replicative senescence" and die by apoptotic death (7,8). Hayflick (4) made this observation in 1965 on human diploid fibroblasts. „They show a spontaneous decline in growth rate on continous culture, related to an increasing number of population doublings, eventually terminating after 50-70 population doublings in a quiscent but viable state" (9). Telomeres (7,8) are a noncoding repetition of hexameric sequences (TTAGGG)n, located at the end of the arm of each chromosome. They protect chromosome ends against fusion, recombination and degradation (10). After each cell division, telomeres shorten because the DNA polymerase cannot replicate the very end of the linear DNA strands („the end replication problem"). In vitro, when telomere length shortens and reaches a critical size, the cell ceases to divide and enters senescence and later dies by apoptotic death. Telomere is the mitotic clock! In progeria (premature old age), for example, there is a shortening of thelomeres. Under oncogenic stimulation, a few cells can overpass senescence and finally stabilize telomere length, allowing cells to divide indefinitely. Telomerase (7,8) is an enzyme able to add de novo telomeric hexamers at the end of DNA strands. It is a reverse transcriptase, ribonucleoproteic complex, consisting of an RNA template (TR) and a catalystic protein (TERT). Telomerase is detected in embryonic cells and stem cells in adults but is absent in most normal somatic cells. It is repressed in normal human somatic cells but is reactivated during cancer progression (11). Its activation through its effect on telomere elongation is required to sustain the indefinite proliferation of cancer cells, i.e. their unlimited life span. Telomerase exists in the majority of human cancer. For example, overexpression of human telomerase RNA is an early event in esophageal carcinogenesis (11). The question arises: is the telomerase expression a prime mover or only a bystander in carcinogenesis. Telomerase is not, per se, a carcinogen. Lymphocytes, for instance, exhibit telomerase activity when activated (7).

B. Apoptosis and cancer cell

The normal cells are dying by necrosis („violent death" as a result of a severe damaging stimulus) but also by apoptosis (12) - programmed cell death („suicide of cell"). Apoptosis is universaly specifically designed in biology to switch off some no more necessary cells and to eliminate them. The morphological characteristics of necrosis are different than that of apoptosis (13). Most apoptotic pathways involve a sensor that detects a death-inducing signal, a signal transduction network, and an execution machinery (caspase enzymes) that actively carries out the process of cell death (14). Cancer cells often ignore or fail to generate the signals that should trigger self-destruction. This feature is specifically assigned to bcl-1, myc and p53 genes (3). The new knoledge about cancer genes and pathways of cancer cell immortalization are great achievement of basic oncology and basis for future anticancer therapy by: gene therapy (replacing the wrong genes) or suppressing the wrong genetic informations on the levels of: transcription, translation or executive proteins; suppression of enzyme telomerase; and inducing apoptosis of cancer cell.

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