Cancer and Immortal Research Literatures

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Abstract: Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This article introduces recent research reports as references in the cancer and immortal related studies.
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1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

The following introduces recent reports as references in the related studies.

Brenner, A. J. and C. M. Aldaz "Chromosome 9p allelic loss and p16/CDKN2 in breast cancer and evidence of p16 inactivation in immortal breast epithelial cells." Cancer Res. 1995 Jul 1;55(13):2892-5.

To define the extent of involvement of chromosome 9p in breast carcinogenesis, we performed microsatellite length polymorphism analysis of markers spanning this region. Of 24 primary breast carcinomas analyzed, we observed a high frequency (58%) of loss of heterozygosity or allelic imbalance affecting subregion 9p21-22. Mutational analysis of CDKN2 (p16) was performed to determine whether this gene was the target of such alterations. Of 21 tumors analyzed, only 1 showed a mutation of probable consequence, suggesting that CDKN2 appears not to be the target of loss of heterozygosity and indicating the possible existence of another tumor suppressor gene within this region. Additionally, since it has been suggested that some CDKN2 deletions and mutations could be due to an in vitro phenomenon, four immortal breast cell lines derived from normal epithelium, MCF10F, MCF12F, 184A1, and 184B5, were examined for loss or mutation of CDKN2. Two lines (MCF10F and MCF12F) showed homozygous deletions of CDKN2, and one (184A1) revealed a hemizygous deletion and a nonsense mutation in the remaining allele. This could imply an important role of CDKN2 in the control of immortalization or in vitro adaptation and is the first evidence of such in nontumor-derived cell lines. Additionally, this is the first report of frequent loss of heterozygosity in the 9p21-22 chromosome subregion of uncultured primary breast tumors.

Bright, R. K., C. D. Vocke, et al. "Generation and genetic characterization of immortal human prostate epithelial cell lines derived from primary cancer specimens." Cancer Res. 1997 Mar 1;57(5):995-1002.

Difficulty in establishing long-term human prostate epithelial cell lines has impeded efforts to understand prostate tumorigenesis and to develop alternative therapies for prostate cancer. In the current study, we describe a method that was successful in generating 14 immortal benign or malignant prostate epithelial cell cultures from primary adenocarcinomas of the prostate resected from six successive patients. Immortalization with the E6 and E7 transforming proteins of human papilloma virus serotype 16 was necessary to establish long-term cultures. Microscopic examination of fresh tumor specimens exhibited a variable mixture of benign and malignant epithelium. Thus, single-cell cloning of tumor-derived cell cultures was essential for defining tumor cell lines. Efforts to characterize these cultures using traditional criteria such as karyotype, growth in nude mice, and prostate-specific antigen expression were noninformative. However, allelic loss of heterozygosity (LOH) represents a powerful alternative method for characterizing tumor cell lines originating from

primary adenocarcinomas of the prostate. Microdissected fresh tumors from four of six patients revealed LOH at multiple loci on chromosome 8p, as assessed by PCR. LOH on chromosome 8p matching the patterns found in microdissected tumors was also observed in a tumor-derived cell line and its clones, as well as in one clone from a tumor-derived cell line from a second patient. LOH was not observed in immortal lines generated from autologous benign prostatic epithelium, seminal vesicle epithelium, or fibroblasts. The multifocal nature of prostate cancer, as well as the presence of an entire spectrum of malignant transformation within individual prostate glands, necessitates this type of careful analysis of derivative cell cultures for their validation as in vitro models that accurately reflect the primary cancers from which they are derived.

Cassoni, P., A. Sapino, et al. "Mitogenic effect of the 15-kDa gross cystic disease fluid protein (GCDFP-15) on breast-cancer cell lines and on immortal mammary cells." Int J Cancer. 1995 Jan 17;60(2):216-20.

The biological significance of a major protein component in the fluid of gross cystic breast disease and a recognized marker of apocrine metaplasia, i.e. the 15-kDa glycoprotein (GCDFP-15), is presently unknown. We have added GCDFP-15 to cell culture medium and tested its effect on proliferation of 4 human breast-cancer cell lines (MCF7, BT474, MDA-MB231 and T47D) and a "normal" human immortal breast-cell line (MCF10A). These breast-cell lines showed a mitogenic response to GCDFP-15 (10 micrograms/ml). GCDFP-15 enhanced cell growth of the MCF10A, MCF7, BT474 and MDA-MB231 cell lines at both 48 and 96 hr of exposure. The glycoprotein exerted a mitogenic effect on the T47D cell line at 48 hr but not at 96 hr. This may be due to an auto-regulatory effect of endogenous GCDFP-15 synthesized by the T47D cells. GCDFP-15 was ineffective on 2 colon-cancer cell lines (HT29 and NIC-H716), on the IMR32 neuroblastoma cell line and on the NIC-H209 small-cell lung carcinoma cells. A separate major breast cystic disease fluid protein of 24 kDa (GCDFP-24) was tested, following the same experimental design, on the 5 breast-cell lines, and showed no mitogenic activity. The mitogenic effect of GCDFP-15 observed in this study in both "normal" and malignant breast epithelial cells suggests a possible relationship between apocrine metaplasia in breast cystic disease and the development of breast epithelial hyperplasia. In addition, a possible role of GCDFP-15 in breast-cancer progression should be considered.

Gagos, S., D. Iliopoulos, et al. "Cell senescence and a mechanism of clonal evolution leading to continuous cell proliferation, loss of heterozygosity, and tumor heterogeneity: studies on two immortal colon cancer cell lines." Cancer Genet Cytogenet. 1996 Sep;90(2):157-65.

Extensive karyotypic analysis was performed on early and late passages of two continuous human cell lines, SW480 and SW620, that were derived from the same colon cancer patient. We cultivated these two cell lines in vitro for a period of 24 months and periodically examined their chromosome constitution. SW480 cells, from passage 138, were injected subcutaneously into 20 nude mice. The tumors that grew in nude mice were then cultivated in vitro for several passages to compare histopathologic findings and tumor growth patterns with clonal chromosomal profiles. Despite some karyotypic diversity, the two cell lines exhibited common marker chromosomes and followed similar patterns of evolution. During subsequent passages, acquisition of new chromosomal abnormalities gave rise to sidelines with a near-diploid genome that frequently underwent endoreduplication. Genomic instability seemed to play an important role in the emergence, growth, and subsequent elimination of the heterogenous sidelines by selection, clonal expansion, and cell death by senescence. Despite continuous growth, both the cell lines occasionally showed telomeric associations and random dicentric and multicentric formations. These lesions were considered evidence of cell senescence and were related to the disappearance of particular sidelines through evolution. Successful evolutionary steps were characterized by elimination of pre-existing marker chromosomes that were subsequently replaced in the karyotype by their cytologically intact homologous chromosomes possibly after selective endoreduplication. Frequent loss of heterozygosity for the chromosomes taking part in this process is postulated. We suggest that one of the mechanisms by which cancer cells bypass senescence may be related to their potential for continuous clonal diversification.

Kim, N. W., M. A. Piatyszek, et al. "Specific association of human telomerase activity with immortal cells and cancer." Science. 1994 Dec 23;266(5193):2011-5.

Synthesis of DNA at chromosome ends by telomerase may be necessary for indefinite proliferation of human cells. A highly sensitive assay for measuring telomerase activity was developed. In cultured cells representing 18 different human tissues, 98 of 100 immortal and none of 22 mortal populations were positive for telomerase. Similarly, 90 of 101 biopsies representing 12 human tumor types and none of 50 normal somatic tissues were positive. Normal ovaries and testes were positive, but benign tumors such as fibroids were negative. Thus, telomerase

appears to be stringently repressed in normal human somatic tissues but reactivated in cancer, where immortal cells are likely required to maintain tumor growth.

Kroemer, G. Cancer: defeating the immortal, Cancer Biol Ther. 2007 Aug;6(8):1324-8. Epub 2007 Aug 13.

My first reaction when I was invited to contribute an article for the section "Profiles and Legacies" of Cancer Biology & Therapy was a shock. Am I that old, at the age of 46 years, that I should write my own obituary? But then I realized that I would have the opportunity to share some of my intimate convictions, dilemmas and doubts. So instead of an auto-apotheosis, this piece will simply translate what I could tell a friend during an after-dinner conversation, knowing that the plans for the future (optimistically) outnumber the experiences in the past.

Winquist, R. J., A. B. Hall, et al. "Evaluating the immortal strand hypothesis in cancer stem cells: symmetric/self-renewal as the relevant surrogate marker of tumorigenicity." Biochem Pharmacol. 2014 Sep 15;91(2):129-34. doi: 10.1016/j.bcp.2014.06.007. Epub 2014 Jun 24.

Stem cells subserve repair functions for the lifetime of the organism but, as a consequence of this responsibility, are candidate cells for accumulating numerous genetic and/or epigenetic aberrations leading to malignant transformation. However, given the importance of this guardian role, stem cells likely harbor some process for maintaining their precious genetic code such as non-random segregation of chromatid strands as predicted by the Immortal Strand Hypothesis (ISH). Discerning such non-random chromosomal segregation and asymmetric cell division in normal or cancer stem cells has been complicated by methodological shortcomings but also by differing division kinetics amongst tissues and the likelihood that both asymmetric and symmetric cell divisions, dictated by local extrinsic factors, are operant in these cells. Recent data suggest that cancer stem cells demonstrate a higher incidence of symmetric versus asymmetric cell division with both daughter cells retaining self-renewal characteristics, a profile which may underlie poorly differentiated morphology and marked clonal diversity in tumors. Pathways and targets are beginning to emerge which may provide opportunities for preventing such a predilection in cancer stem cells and that will hopefully translate into new classes of chemotherapeutics in oncology. Thus, although the existence of the ISH remains controversial, the shift of cell division dynamics to symmetric random chromosome segregation/self-renewal, which would negate any likelihood of template strand retention, appears to be a surrogate marker for the presence of highly malignant tumorigenic cell populations.

Zajchowski, D. A., V. Band, et al. "Suppression of tumor-forming ability and related traits in MCF-7 human breast cancer cells by fusion with immortal mammary epithelial cells." Proc Natl Acad Sci U S A. 1990 Mar;87(6):2314-8.

Somatic cell hybrids between MCF-7 human breast cancer cells and normal immortalized human mammary epithelial cells have been obtained by polyethylene glycol-mediated cell fusion. The hybrid cells are suppressed in their ability to form tumors in nude mice, as well as in traits specific to the tumorigenic MCF-7 parent: growth factor independence, tumor necrosis factor sensitivity, and pS2 gene expression. In addition, they display other characteristics of the "normal" parent, including increased expression relative to the MCF-7 cells of the genes for the extracellular matrix component fibronectin, the intermediate filament keratin 5, and the angiogenesis inhibitor thrombospondin. The levels of keratins 8 and 18 also resemble those of the nontumorigenic parent. These results provide evidence for the existence of tumor suppressor gene products in immortal mammary epithelial cells. We propose a characteristic "suppressed" tumor cell phenotype, which encompasses altered cytoarchitecture, angiogenesis capabilities, and growth factor requirements.

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

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