Original Research Article

Tumor Cells and Diseases Related to Drug Treatment

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ABSTRACT

At present, tumors especially malignancies, have become one of the most serious diseases that threaten human health. The use of chemotherapy, radiotherapy, surgery, biotherapy and integrated traditional Chinese and Western medicine is the most effective means of treating tumors. Among them, the application of new anti-tumor drugs, in improving the quality of life of cancer patients to extend the survival time, delay the development of the disease has played a huge role. In this paper, we reviewed the related research progress of tumor cells from the aspects of tumor features, related signal pathways, related genes, epigenetic modification, tumor stem cells and tumor microenvironment, so as to have a more comprehensive understanding of tumor and cell apoptosis.

KEYWORDS: antitumor drug development cell apoptosis tumor cell carcinoma gene tumor stem cell

Introduction

Animals in vivo due to split regulation and loss of control and infinite proliferation of cells called tumor cells (tumor cell). Transmissible tumors are called malignancy, and malignant tumors of epithelial tissue are called carcinoma. At present cancer cells have been used as a common name for malignant tumor cells.

The occurrence of tumor and apoptosis disorders are closely related. Lack of apoptosis, decreased apoptosis sensitivity is the main cause of tumorigenesis. The discovery of tumor cell apoptosis mechanism will be important for the cure of cancer. So the mechanism of apoptosis, related genes, signal pathway research is particularly important.

April 17, 2010, is the 16th 'World Cancer Day'. Tumor is the body in a variety of tumorigenic factors, local tissue abnormal proliferation of cells and the formation of new organisms, often manifested as local mass. Tumor cells have abnormal morphology, metabolism and function. It grows strong, often continuous growth. Cancer is a group of diseases characterized by loss of control of abnormal cells and spread from the primary site to other parts, such as uncontrollable, infringing vital organs and causing failure, leading to death. Malignant tumors derived from epithelial tissue are called cancer, and malignant tumors derived from mesenchymal tissues (including connective tissue and muscle) are sarcoma.

Into the 21st century, with the development of modern medicine and molecular mechanism of cancer research gradually deepening, the global anti-tumor drug research and development fruitful. Since 2005, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) officially approved the listing of 24 anti-cancer drugs (except for orphan drugs). According to incomplete statistics, in 2010 the world is in the clinical research stage of anti-tumor drug more than 470, involving a total of more than 2760 clinical studies, of which 231 clinical trials of 231, involving more than 50 new drugs. [1]

1.　The characteristics of the tumor

It is generally believed that the tumor has the following five characteristics: cell growth and division of loss of control, with invasive and diffuse, intercellular interaction changes, mRNA expression profile and protein expression profile or protein activity changes and in vitro culture of malignant transformation characteristics.

The latest view is found in the March issue of the new magazine, Professor Weinberg published a new review: Hallmarks of Cancer: The Next Generation, the article has the following ten characteristics of the tumor: self-sufficiency in the growth signal (Self-Sufficiency in Stress resistance, Antistroptic Signs, Resisting Cell Death, Limitless Replicative Potential, Sustained Angiogenesis, Tissue Invasion and Metastasis, (Tissue Invasion and Metastasis);

Avoiding Immune Destruction; Promote Tumor Promotion Inflammation; Deregulating Cellular Energetics; Genome Instances and Mutation.

2.   The tumor-related genes

At present, the mechanism of tumor-related genes can be explained as: proto-oncogene is activated (such as src gene causes chicken sarcoma and Ras gene), tumor suppressor gene inactivation (such as Rb gene inactivation, p53 gene) Gene is a DNA nucleotide sequence that promotes malignant transformation of cells. According to the function of protein, it can be divided into the following five categories: growth factor; growth factor receptor and protein kinase (especially tyrosine protein kinase); GTP Binding protein; nuclear protein (generally refers to the DNA binding protein); other, such as erb-A gene can express thyroid / steroid hormone receptor, crk gene can express phospholipase C and so on.

2.1.   Ras gene

Is a proto-oncogene, when activated, increased expression, inhibition of apoptosis, and promote cell proliferation. Immunohistochemistry can detect both mutant and wild-type protein, and need to be further detected by detecting mRNA level.

2.2.   Bcl-gene family

Is a proto-oncogene, including genes that promote apoptosis, such as Bax, Bad, Bak, Bclxs, and genes that inhibit apoptosis, such as bcl-2, bcl-xl, Mcl-1, AL and Bag. Bax can form homologue (Bax / Bax), promote cell apoptosis; also with Bcl-2 formation of heterodimer (Bax / Bcl-2), the ratio of the two affect the rate of apoptosis. Bcl-2 serine -70 site phosphorylation can be inactivated, increased apoptosis [].

2.3.   C-myc gene

Is a proto-oncogene, which encodes a protein that is itself a transcriptional regulator that has a dual role in the presence of certain growth factors (such as insulin-1 and IL-2) that promote cell proliferation without the presence of growth factors Apoptosis

2.4.   Fas gene

Is a proto-oncogene, which encodes a transmembrane protein that is a cell surface, the Fas antigen (also known as death receptor, APO-1, CD95), and its ligand to promote apoptosis [].

Other proto-oncogenes such as c-fos, c-jun, c-erb B2, IGF- and so on, tumor suppressor genes such as Rb gene, P16 gene, directly or indirectly involved in the regulation of apoptosis.

Tumor suppressor gene, some produce can inhibit tumor formation and development of factors, can be divided into four categories:

antagonist of oncogene products (transcriptional negative control region of C-myc gene 5 '); interferon; somatostatin; factors that control chromosomal stability (such as Rb gene and WiLms tumor-related gene Wg).

P53 gene is a tumor suppressor gene, encoding relative molecular mass of 53000 nuclear phosphoric acid protein. Wild-type P53 is a negative regulatory gene for cell growth. When the cell DNA is damaged, the cell growth is stopped at G1 phase, and DNA damage is repaired before entering the cell cycle. If the repair fails, the cell is activated to eliminate the damaged cell The Mutant P53 loss of this monitoring ability, in the case of DNA damage, inhibition of apoptosis, promote cell proliferation, resulting in poor prognosis of the tumor. Mutant P53 is more stable than wild-type, long-lived, often mutated P53 protein, or wild-type and mdm2-binding proteins detected by immunohistochemistry or other methods.

SPOP gene this gene is located at the site of human chromosome 17q21, with high deletions and LOH in tumor cells. More importantly, the researchers also found that SPOP tumor suppressor genes were significantly different in tumor cells and mouse animals Inhibition of tumor growth and diffusion function, further studies of its molecular mechanism show that SPOP as a ubiquitin ligase is through the ubiquitination and degradation of malignant tumor protein SRC-3 / AIB1 in the tumor level, which play a role in inhibiting tumor Features. Which will help scientists to further understand the mechanism of breast cancer, the future may also be used for tumor diagnosis.

C2myc, c2fos and c2jun c2myc genes encode an unstable, highly conserved phosphoprotein. Which is located in the nucleus, can be combined with DNA and non-histone, with cell proliferation or promote the role of cell apoptosis. In the presence of growth factors, c2myc can promote cell proliferation, no growth factor, then accelerate the apoptosis. C2fos

as proto-oncogene, expression product c2Fos, Consuelo and other studies that c2Fos is not an essential component of apoptosis, apoptosis may be a side effect.

3.   The tumor related to the signal pathway

The signal pathways associated with tumorigenesis include JAK-STAT signaling pathway, p53 signaling pathway, NF-κB signaling pathway, Ras, PI (3) K and mTOR signaling pathway, Wnt signaling pathway, BMP signaling pathway and so on.

P53 tumor suppressor gene is a cellular molecular signaling cascade to guide the occurrence of lethal DNA damage in cells to carry out the key to self - destruction, a variety of signal factor regulation. If the p53 gene is inactivated (as seen in more than half of human cancers), the detection and balance of cell growth cannot be carried out and somatic cells begin to accumulate mutations that eventually lead to cancer. P53 plays a very important role in many apoptotic signaling pathways, including membrane apoptosis signal, mitochondrial apoptotic pathway, and it affects many transcription and expression of apoptosis-related factors in the nucleus. For example, when DNA damage or cell proliferation in cells is abnormal, the p53 gene is activated, resulting in cell cycle arrest and initiating a DNA repair mechanism to repair the damaged DNA. However, when DNA damage is excessive and cannot be repaired, p53 as a transcription factor can further activate the transcription of downstream apoptotic genes, induce apoptosis and kill cells with DNA damage. Otherwise, the DNA damage to the cells may gradually out of the normal regulation, may eventually form a tumor. A new mouse model created by the researchers at the latest Salk Institute of Biology shows that researchers' information on the regulation of p53 activity obtained from in vitro studies may not be applicable to living, breathing organisms. This study suggests that regulatory information about p53 genes previously obtained by tissue culture methods may not be an important regulatory form in living organisms, thus increasing awareness of p53 genes.

In recent years, studies have shown that PI3K-Akt can inhibit cell apoptosis in a variety of ways and promote cell survival. PI3K-Akt signaling pathway anti-apoptotic mechanisms are: direct regulation. Apoptosis of mammalian cells is a multicarrier reaction process. play a role in cell survival by directly or indirectly affecting the transcription factor family (Forkhead, NF-κB and p53). through the regulation of cell cycle affect cell proliferation. to prevent mitochondrial release of apoptosis factors.

Histone acetylation is a common epigenetic modification. High levels of histone acetylation in the promoter region of the gene often promote the expression of the gene. Abnormal histone acetylation is closely related to various pathological processes. HDAC is an important histone acetylation regulator, and their expression in many cancer tissues is too high. Their inhibitors can effectively induce apoptosis of cancer cells from different tissues, but at the same concentration, the toxicity of normal cells is very small, so it is a kind of potential new anticancer compounds with good application prospect. Embryonic cancer cells (embryonic carcinoma cells) malignant teratoma tissue differentiation is low, high degree of malignant cells that part of the cells. They play an important role in the recurrence and metastasis of teratomas. Traditional chemotherapy drugs for the treatment of such cancer cells is not ideal. Studies have shown that HDAC inhibitors can effectively induce apoptosis of embryonic cancer cells, but it is not clear which molecular mechanisms.

Shanghai Institute of Biochemistry and Cell Biology Song Jianguo research group doctoral scholar Shu Guangwen and others research work shows that the expression of Zac1 gene up-regulation in histone deacetylase (histone deacetylase) (HDAC) inhibitor-induced apoptosis of embryonic cancer cells Plays a key role.

4.   Cancer stem cells

1994 Lapidot et al. isolated human leukemic stem cells (LSC) for the first time by specific cell surface markers. It was found that only LSCs had the effect of self-renewal and maintenance of their malignant phenotypes, demonstrating the objective presence of tumor stem cells. Recently, breast cancer and brain tumors have been isolated and purified with a specific surface markers of tumor stem cells to create a solid tumor stem cell research of the new situation and put forward the solid tumor is also a stem cell disease concept. Study the prevalence of tumor stem cells and explore its mechanism, is still the current tumor biology research is a very important issue.

5.   Cytotoxic drugs

Cytotoxic drugs are classic antineoplastic agents, the efficacy of certain. Although its side effects are greater, but because of the lack of alternative drugs, has been the basic drug of chemotherapy. The main categories are the following:

5.1. Alkylating agent

Trabectedin (Trabectedin) is the first marine source of antineoplastic agents, for the extraction of quaternary tetrahydroquinoline alkaloids in the semi-synthetic products. In addition to blocking the differentiation of tumor cells in the G1 / G2 cycle, the secretion of vascular endothelial growth factor (VEGF) and the expression of VEGF receptor (VEGFR) - 1 can be inhibited. In 2004, it in Europe, the United States has been designated as the treatment of acute lymphoblastic leukemia, soft tissue sarcoma and ovarian cancer orphans. In 2007, EMEA formally approved its second-line treatment for advanced soft tissue sarcoma.

5.2. Antimetabolites

Nelarabine (GlaxoSmithKline) is a prodrug of deoxyguanosine analogue 9- [beta] -carboxoguanine (ara-G), activated in vivo to 5-triphosphate ara-GTP, selective to accumulate in T cells to inhibit DNA synthesis, leading to cancer cell death. Anti-folic acid preparation Pralatrexate (Allos Pharmaceuticals) is made from methotrexate to inhibit dihydrofolate reductase. In 2009, the US FDA approved its single use for recurrent / refractory T-cell lymphoma treatment, administration of regular intramuscular injection of vitamin B12, daily oral folic acid can reduce the treatment-related hematologic toxicity and mucositis.

5.3. Platinum anti-tumor drugs

Tetraplatin (Satraplatin, Bristol-Myers Squibb) is a third-generation platinum complex with a cyclohexylamine structure. Oral administration of good absorption, efficacy and cisplatin, carboplatin similar, and cisplatin no cross-resistance, adverse reactions for vomiting, no kidney, liver and neurotoxicity. At present, prostate cancer, small cell lung cancer (SCLC) and non-SCLC (NSCLC), ovarian cancer for stage clinical trials.

5.4. Anthracycline antitumor drugs

Pixantrone (Pixantrone, Cell Therapeutics) is a mitoxantrone derivative, its mechanism and mitoxantrone similar, can be embedded in cell DNA, inhibition of topoisomerase (Topo). The complete remission rate for NHL treatment was about 20%, and 59% in combination therapy.

Amrubicin (Amrubicin, Sumitomo Pharmaceutical) is the third generation of synthetic anthracycline analogues, and doxorubicin mechanism of action is slightly different, mainly by inhibiting Topo activity, and ultimately lead to DNA breakage and inhibition of tumor cells proliferation. Was approved in Japan in 2002 for the treatment of NSCLC and SCLC. In 2008, the US FDA granted its SCLC orphan eligibility.

5.5. Microtubule Stabilizer

At present, the clinical application of the main taxane and vinblastine compounds, the newly developed microtubule stabilizer is divided into four categories: terpenoids (taxanes), macrolides (such as epothilone, Escupolide), polyhydroxy tetraoleactones and steroids.

Taxane on behalf of the product paclitaxel since 1992 by the US FDA officially approved the listing, has been approved in more than 40 countries, mainly for breast cancer, ovarian cancer and NSCLC first-line treatment. However, the low solubility of paclitaxel, low effective utilization and P-glycoprotein-related drug resistance and other issues limit its clinical application. Therefore, the taxane-related research is mainly paclitaxel new formulations and the development of new compounds in two aspects.

Nano-paclitaxel (Capxol, USA) is the first approved non-dissolving nano-protein-binding granule chemotherapeutic agent. The preparation of human serum albumin as a copolymer of paclitaxel to form nano-suspension, the use of albumin receptor internal transmission of drugs through the tumor neovascular endothelial cell wall, so that paclitaxel direct access to tumor stroma. Phase III clinical trials show that compared with paclitaxel, paclitaxel efficacy can be increased by 1 times, and significantly extend the PFS and overall survival, well tolerated.

6. The treatment of tumor cells

6.1. endocrine therapy

Into the 21st century, there are a number of tumor endocrine therapy drugs listed, in addition to the market has entered the market of leuprolide acetate (2000), Qu Pui Ruilin (2001), has been listed in the foreign or upcoming Fluffies (Fulvestrant, AstraZeneca), Abarelix (Praarelis Pharmaceuticals), Degarelix, Group Amrinlin (Vantas, Villea Pharmaceutical Company) and so on.

Fulvestrant is a novel estrogen receptor antagonist that binds, blocks and degrades estrogen receptors in breast cancer cells and has no agonistic effect on estrogen receptors. April 2002 and October were listed in the United States and the European Union, for the anti-estrogen drug treatment of postmenopausal hormone receptor-positive metastatic breast cancer, is the first can be used for advanced tamoxifen refractory breast cancer treatment Of the anti-estrogen drugs, once a month intramuscular injection, with good compliance. Injection of barakek suspension for gonadotropin-releasing hormone antagonists, in 2003 the US FDA approved for the application of luteinizing hormone-releasing hormone (LHRH) agonist therapy and refused to undergo surgery for patients with advanced prostate cancer Palliative therapy, its role is characterized by strong and fast castration effect. Compared with leuprolide, although the reduction of serum prostate specific antigen (PSA) and maintain the level of testosterone castration is equivalent, but the role of faster and more effective.

6.2.　Immunotherapeutic drugs

In recent years, with the continuous enrichment of immunology theory, immunology technology continues to introduce new, tumor antigens, especially T cell recognition of tumor antigens have been found to antibody therapy, T cell therapy and tumor vaccine as the representative of the tumor immunotherapy has been made significant progress. Immune cells CD4 are T cell markers that are expressed in most T cell lymphomas.

Zanolimumab (HuMax-CD4, Humax) is a humanized anti-CD4 monoclonal antibody. An ongoing interim trial of phase II clinical trials suggests that the drug treated 21 patients with refractory recurrent CD4-positive peripheral T-cell lymphoma (PTCL) with a response rate of 23.8%. The study of the T cell lymphoma phase III is underway. CD20 is a type II calcium channel transmembrane protein on the surface of B cells, overexpressed in B cell lymphoma, hairy cell leukemia and chronic B lymphocytic leukemia.

Tumor vaccine is a direct use of tumor antigens for active immunotherapy of a method, early approval of the listed cancer vaccine mainly bladder cancer vaccine, colon cancer vaccine and melanoma vaccine. Recent vaccines are Gardasil (Merck, 2006) and Cervarix (GlaxoSmithKline, 2007), all of which are cervical cancer vaccines. Gardasil can prevent human papillomavirus (HPV) 6,11,16,18 infection for up to 5 years, reduce the incidence of cervical cancer; Cervarix can effectively prevent HPV16 / 18 infection for 4.5 years. [5]

6.3.　Gene therapy drugs

(Formerly known as Rexin-g, Yipei Si Biotechnology Co., Ltd.) is the world's first approved gene carrier nanoparticles (2003, the US FDA approved for the treatment of pancreatic cancer rare Drugs), nanoparticles consisting of the outer layers of the package, the matrix, the shell, the various enzymes and the genetic material, can release deadly kill components, selectively kill cancer cells and block their associated blood supply Do not damage normal cells and healthy tissue, which can reduce the harm of the tumor on the human body, prolong survival and improve the quality of life of patients. Has a very high curative effect on cases of other drug treatment, including targeted biological agents.

6.4.　Target Antitumor Drugs

1 Tyrosine kinase inhibitor

Protein tyrosine kinase (PTK) is the most common growth factor receptor for many kinds of tumors. Inhibition of its activity can destroy the signal transduction of tumor cells, inhibit tumor cell proliferation and neovascularization, but have little effect on normal cells. Common receptor types include the epidermal growth factor receptor (EGFR) family, the insulin receptor (IGFR) family, the platelet-derived growth factor receptor (PDGFR) family, the VEGFR family, the fibroblast growth factor receptor (FGFR) family, and the like. Non-receptor type includes SRC, ABL, JAK, ACK, CSK, FAK, FES, FRK, TEC, SYK family and so on.

2 Mammalian rapamycin target protein inhibitor

The mammalian rapamycin target protein (mTOR) is a Ser / Thr kinase, which belongs to the PIKK superfamily and plays an important role in regulating cell cycle and protein synthesis. It is closely related to the occurrence and development of various tumors. MTOR has become a popular target for cancer therapy.

3 Other targeted anti-tumor drugs

Merck Vorinostat (trade name: Zolinza) is the world's first histone deacetylase inhibitor (HDACI), and another HDACI is Gloucester's Romidepsin (trade name: Istodax). The two drugs were approved by the FDA in 2006 and 2009 for the treatment of skin T lymphoma.

Bristol-Myers Squibb's Tanespimycin is the first heat shock protein inhibitor (HSPI) to enter clinical studies and has now entered Phase II / III clinical studies of multiple myeloma.

7.   Conclusions

From the simple malignant proliferation to oncogene proto-oncogene, to the relevant signal transduction system, tumor stem cells, with the development of science, people's understanding of tumor cells is also a step by step deepening, the relevant treatment is also continuous progress. Cancer vaccines, gene knockout, repair and other terms are also emerging. Apoptosis as an important component of programmed cell death plays an important role in cell life. The study of the mechanism of tumor cell apoptosis and the decrease of sensitivity will undoubtedly play an important role in the control and cure of tumor cells. On the whole, with the gradual emergence of the mechanism of tumor, I believe that specific drugs for tumor cells will continue to market, the quality of life of cancer patients will be significantly improved, and even long-term survival with tumor is also possible, the tumor may be like diabetes, Blood pressure as a controlled chronic disease, and the body long-term peaceful coexistence.

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