

Research progress of targeted drugs in tumor therapy

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Abstract. With the development of The Times, people have a deeper understanding of cancer cells, while explaining the related carcinogenic mechanism, cancer treatment drugs have also been developed accordingly, and more and more new anticancer drugs have been developed. Cancer generally refers to malignant tumors, which is caused by malignant cell proliferation and is invasive and metastatic. Targeted drug therapy is one of the means of malignant tumors, and also an important method to achieve breakthrough effect of malignant tumors. Targeted drugs are mainly divided into two categories, one is monoclonal antibody, the other is single target or multi-target small molecule inhibitors. In recent years, we promote tumor treatment, and obtain huge clinical benefits. Targeted drugs can also be expensive while exerting their therapeutic advantages, and the long-term use of targeted drugs can easily cause the limitations such as drug resistance, toxic and side effects. In short, compared with traditional surgical treatment, radiotherapy, chemotherapy and other means, targeted drugs have significant therapeutic advantages but also have many limitations. With the development of technology, proteomics, genomics and so on, targeted drugs also have great development prospects.

Keywords: Targeted therapy, EGFR, PD-1, VEGF, HER-2.

1. Introduction

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. Cancer can start almost anywhere in the human body, which is made up of trillions of cells. Normally, human cells grow and multiply (through a process called cell division) to form new cells as the body needs them. When cells grow old or become damaged, they die, and new cells take their place. Sometimes this orderly process breaks down, and abnormal or damaged cells grow and multiply when they shouldn't. These cells may form tumors, which are lumps of tissue. Tumors can be cancerous or not cancerous (benign). Cancerous tumors spread into, or invade, nearby tissues and can travel to distant places in the body to form new tumors (a process called metastasis). Cancerous tumors may also be called malignant tumors. Many cancers form solid tumors, but cancers of the blood, such as leukemias, generally do not. Benign tumors do not spread into, or invade, nearby tissues. When removed, benign tumors usually don't grow back, whereas cancerous tumors sometimes do. Benign tumors can sometimes be quite large, however. Some can cause serious symptoms or be life threatening, such as benign tumors in the brain.

Cancer is a genetic disease—that is, it is caused by changes to genes that control the way our cells function, especially how they grow and divide. Genetic changes that cause cancer can happen because: of errors that occur as cells divide, of damage to DNA caused by harmful substances in the environment, such as the chemicals in tobacco smoke and ultraviolet rays from the sun. (Our Cancer Causes and Prevention section has more information) they were inherited from our parents.

The body normally eliminates cells with damaged DNA before they turn cancerous. But the body's ability to do so goes down as we age. This is part of the reason why there is a higher risk of cancer

later in life. Each person's cancer has a unique combination of genetic changes. As the cancer continues to grow, additional changes will occur. Even within the same tumor, different cells may have different genetic changes.

Molecular targeted drug therapy is a special molecular target for different tumors, which is different from the traditional mechanism and side effects of traditional chemotherapy. The effect of monomer therapy is mild to other cellular side effects. Targeted therapeutic drugs are generally divided into two categories: small molecular targeted drug oral dosage form and monoclonal antibody injection form. Small molecular targeted drugs are usually used to block the signal transduction pathway necessary for tumor growth and proliferation, inhibit tumor growth, and cause tumor cell extinction. Although macromolecular monoclonal antibodies, that is, monoclonal antibody drugs and small molecular targeting drugs act on signal pathways, the blocking of macromolecular monoclonal antibodies can be seen as blocking "signal transmission", while small molecular targeting drugs block "signal reception". Antibody drugs block the issuance of tumor proliferation instructions to prevent tumor growth, and some cooperate with chemotherapy to further kill and die out tumor cells in order to achieve a better therapeutic effect [1].

Targeted drugs also have some drawbacks. Firstly, targeted drugs are selective, and genetic testing should be performed before using targeted drugs. Targeted therapy can only be performed if a suitable therapeutic target is detected. For targeted drugs that must find therapeutic targets, if genetic testing does not detect a suitable target, and blind use of targeted therapeutic drugs will not only fail to treat, but also delay the opportunity of using other methods, so that further the spread of tumor and severe metastasis will be life-threatening. Secondly, there will still be some adverse reactions in the process of targeted therapy. Even if the adverse reactions of the use of targeted drugs will be smaller than those of chemotherapeutic drugs, there will be adverse reactions different from those of chemotherapeutic drugs. For example, targeted drugs can cause serious rash and diarrhea, and some drugs can cause adverse reactions such as hypertension, proteinuria, HFSR and other adverse reactions, which need to be paid close attention to in the treatment process and actively treated after discovery. Targeted drug resistance is a thorny problem in the development process of targeted drugs and in cancer treatment. With the growth of the time of using targeted drugs, the human experience has a certain drug resistance that makes the therapeutic effect weaken or lose the therapeutic effect. Generally, targeted drugs will show drug resistance after taking them for about a year, greatly reducing the effect of drug treatment. At the same time, the expensive price of targeted drugs will have a great economic burden on patients' families. At present, targeted drugs are expensive and need to be taken every day. Generally, they are taken for more than one month first. If the drug is found to be effective for patients, they should be taken for a long time until drug resistance occurs. So only a small number of families can withstand targeted therapy.

Targeted drug therapy works by targeting specific molecules needed for cancer or tumor growth, rather than the usual conventional chemotherapy that targets all continuously dividing cells. A drug therapy that stops the growth of cells. Targeted cancer therapies are believed to be more effective and less harmful to normal cells than other currently available treatments. Targeted therapies can treat breast cancer, multiple myeloma, lymphoma, prostate cancer, melanoma, thyroid cancer, and some other cancers. Targeted drugs are much more effective than chemotherapy and have fewer side effects, but targeted therapy has some limitations: prone to drug resistance, target specific, but structural and Designing drugs for functional regulation is challenging. Oncogenesis and development is a multi-gene, multi-step, and complex biological process. Molecular typing of oncogenes to guide clinical targeted drug therapy using bioinformatics research methods has opened new avenues in cancer therapy. Recently, drugs that target different types of cancer have also become popular.

2. EGFR Targeted drug

EGFR (epidermal growth factor receptor), also known as ErbB1 and HER1, is a common tyrosine kinase receptor. In natural physiology, it can be found that EGFR signaling pathway plays an

important role in physiological processes such as cell growth, proliferation and differentiation. EGFR is often regarded as one of the proto-oncogenes because of its role in promoting cell proliferation and anti-apoptosis. EGFR gene is located on chromosome 7 long arm Q22, which contains 28 exons and encodes EGFR protein. Under normal conditions, the EGFR family is important for animal embryonic development, involving brain, skin, stem cells, lungs, stomach and other tissues. To explore the essence, EGFR is a transmembrane glycoprotein expressed on the surface of epithelial cells, which binds to specific ligands to activate, thus regulating a variety of pathways, in which Ras/Raf/MAPK and JAK/STAT play an indispensable role in cell survival, proliferation, development and metastasis.

2.1. Relationship

When normal EGFR is affected by a large number of carcinogenic factors, gene mutation occurs and its behavior changes, and the receptor continues to attract epidermal growth factor protein to the cell surface to form a tumor, while another case is EGFR gene amplification, that is, overexpression occurs, and excessive receptors appear on the cell surface, resulting in abnormal growth and proliferation of cells, which not only induces the transformation of malignant tumor cells. It also provides survival conditions for malignant tumor cells. On the other hand, EGFR plays an important role in the spread of tumor cells. It can inhibit tumor cell apoptosis, promote angiogenesis, stimulate cell movement and invasion, and accelerate the progress and metastasis of tumor cells. However, in the process of signal transduction of EGFR, tyrosinase, a "lubricant" protease, is needed. The targeted treatment direction of EGFR is to remove this "lubricant", so that EGFR affected by carcinogens will not play a malignant carcinogenic role. In the mechanism of tumorigenesis, the main signal pathways of EGFR are Ras/Raf/MEK/ERK/MAPK pathway, PI3K/Akt (PKB) pathway and JAK/STAT pathway (see figure 1). At present, the EGFR-targeted drugs are targeted at the corresponding targets, thus interfering with the operation of these signal pathways, in order to treat and inhibit malignant tumor cells.

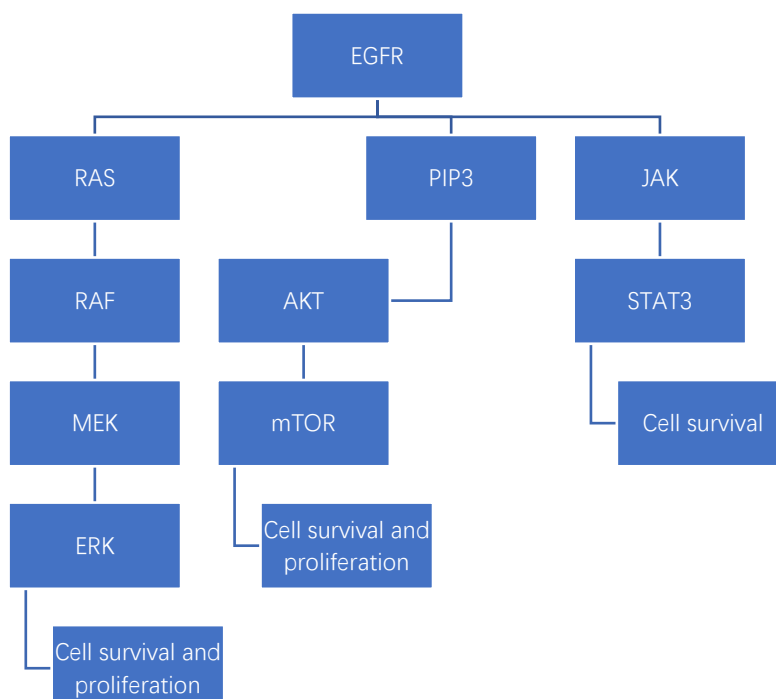


Figure 1. Operation Pathway [2].

2.2. Mutant types

EGFR is the most common mutation, and the main mutation in exon 21 in 18je, 19jol, 20je. G719X is a common subtype of EGFR18 exon mutation, which can be divided into five types. Exon 18 encodes the 719th amino acid. The mutation of a codon in mRNA causes the coding amino acid to change from glycine G to alanine A, cysteine C, aspartic acid D, valine V or serine S. The most common lesion of EGFR19 exon is deletion mutation, that is, Del19. The common mutation types are 2235-2249del15 and 2236-2250del15, accounting for 74%, which is reflected by the deletion mutation of polynucleotide in exon EGFR19, which is a part of EGFR protein responsible for inhibiting its activity. The most common lesion of EGFR20 exon is insertion mutation, which shows that the insertion ratio of exon 20 of EGFR gene is about 4%. Most of them are inserted after M766 amino acids. The classic mutation in exon EGFR21 is L858R, which is reflected in the fact that exon 21 of EGFR encodes the 858th amino acid because codon T at codon 2553 in mRNA is replaced by G, which makes the coding amino acid change from leucine L to arginine R. EGFR19 exon deletion mutation and EGFR21 exon L858R mutation can be classified as EGFR sensitive mutation with the best effect of targeting drugs, also known as "golden mutation", which can be treated with EGFR-TKIs. EGFR18 exon G719X mutation can be treated with second-generation EGFR-TKIs have targeted drugs, and the remission rate is as high as 75% in the investigation, and the effect is similar to that of sensitive mutations. However, the insertion mutation of exon EGFR20 has been a difficult problem for a long time. The first-generation drugs are almost ineffective and the second-generation drugs are less effective. At present, the third-generation EGFR-TKIs the best curative effect and the relative drug duration is longer.

2.3. EGFR targeting drugs

The mechanism of targeted therapy for non-small cell lung cancer (NSCLC) by inhibiting the communication of EGFR-related transduction signals also stems from the inhibition of tumor proliferation by epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKIs). The first-generation EGFR targets gefitinib, erlotinib and erlotinib, and the common characteristics of the three primary targeting drugs can be summarized as effective targeting drugs only for exon 19 deletion mutation and exon 21 mutation, while the second-generation EGFR targeting drugs are alaphatinib and dacomitinib, which are irreversible inhibitors of tyrosine kinase and can effectively target sensitive and moderately sensitive mutations as well as some rare mutations. The third generation of EGFR targeting drugs, based of the first generation of targets, added two kinds of targeting drugs that can effectively inhibit the T790M mutation in exon EGFR20, which are osimertinib and amivantamab respectively. Among many EGFR targeting drugs, the first-generation EGFR-TKIs gefitinib is the earliest selective EGFR receptor inhibitor, and its action pathway is the classical PI3K/Akt/mTOR pathway, in which PI3K (phosphatidylinositol kinase) is a dimer composed of regulatory subunit P85 and catalytic subunit p110. When PI3K binds to growth factor receptor, it can change the protein structure of Akt and activate it, and activate or inhibit a series of downstream substrates such as apoptosis-related protein Bad, Caspase9 activity by phosphorylation, thus regulating protein synthesis, vascular cell growth, inflammation and so on. The mechanism of gefitinib is to competitively inhibit the binding of EGFR to the Mg-ATP site of EGFR-TK catalytic region [3], block EGFR signal transduction, delay the inhibition of tumor cell proliferation, and induce NSCLC apoptosis after competitive binding.

3. PD-1 antibody

PD-1, also known as CD279, is a type I transmembrane glycoprotein composed of 268 amino acids and an important immunosuppressive molecule. PD-1 is a member of the amplified CD28 / CTLA-4 family of T cell regulators with 20% identity to CTLA4. The structure of its protein includes the extracellular IgV domain, followed by transmembrane regions and an intracellular tail. Mature human

PD-1 consists of a 148-amino-acid extracellular region (ECD) and an immunoglobulin-like type V domain, a 24-amino-acid transmembrane domain, and a 95-amino-acid cytoplasmic region. The intracellular tail contains the N terminus involved in constituting an immune receptor tyrosine repression motif (ITIM) and the C terminus involved in constituting two independent tyrosine residues in the immune receptor tyrosine conversion motif (ITSM), suggesting that PD-1 negatively regulates T cell receptor TCR signaling. This is consistent with the binding of SHP-1 and SHP-2 phosphatases to the cytoplasmic tail of PD-1 after ligand binding and, in addition, PD-1 binding to ligand upregulates the E3-ubiquitin ligases CBL-b and c-CBL, triggering T cell receptor downregulation and inhibiting T cell activation and cytokine release. PD-1 is expressed on the surface of activated T cells, B cells, and macrophages, suggesting that PD-1 more generally negatively modulates immune responses [4]. PD-1 regulates the immune system and promotes self-tolerance by downregulating the immune system in response to human cells, as well as by inhibiting T-cell inflammatory activities. This can prevent autoimmune diseases, but it also does not avoid preventing the immune system from killing cancer cells.

3.1. Relationship between PD-1 and Cancer

PD-1 can regulate the activity of T cells in tumor tissues. PD-1-L1, the ligand of PD-1, will be expressed in some cancer cells. The binding of activated PD-1 antibody to PD-L1 on tumor cells causes coloxine phosphorylation in the ITSM domain of PD-1, thus causing dephosphorylation of downstream protein kinases Syk and PI3K, inhibiting the activation of downstream AKT, ERK and other pathways, and ultimately inhibiting the transcription and translation of genes and cytokines required for T cell activation, T cells, and activity of tumor cell proliferation. The present study revealed that the PD-1 pathway is a cancer immune escape.

Tumor cells and the tumor microenvironment then upregulate PD-L1 expression and bind to PD-1 on the surface of the tumor-specific CD8 + T cells to limit the host immune response. IFN-unregulated PD-L1, whereas CD8 + T cells unregulated PD-L1 expression and PD-L1 expression [5].

Studies have shown that EGF stimulates the MAPK and PI3K / mTOR pathways to increase the levels of phosphorylated ERK 1,2 (pERK1 / 2) and phosphorylated ribosomal S6 protein (pS6), and IFN greatly increases the levels of STAT1 and phosphorylated STAT1 (pSTAT1). So EGF and IFN activated the MAPK, PI3K / mTOR, and STAT1 pathways, while increasing the PD-L1 mRNA, protein, and membrane levels, and EGF increased the IFN-induced PD-L1 expression in NSCLC cells. The EGFR effectively enhanced the EGF-dependent MAPK and PI3K / mTOR signaling pathways, and moderately increased the IFN-induced up-regulation of the (p) STAT1. This suggests that the EGFR is an EGF- and IFN-induced CD274 mRNA- and PD-L1 protein- and membrane-level-dependent-mediated signaling. Activation of the MAPK pathway thus promotes the up regulation of PD-L1 induced by the growth factors IFN and PBM. C.

The amplification of the gene encoding PD-L1 (9p 24.1) also up regulates PD-L1 expression, and the PD-L1 gene amplification is mainly attributed to the amplification of chromosome 9p24.1, copy number change, or 9p polyploidy. In addition, the induction of EB virus and epigenetic mechanisms can also cause the up regulation of PD-L1 expression [6].

Because PD-1 is only expressed in activated T cells, inhibitory signaling from PD-1/PD-L1/2 acts only on T cells that have identified tumor antigens and generated tumor-specific responses, where the PD-1/PD-L1/2 pathway mediated "tumor-specific selective T-cell inhibition". Application of PD-1 immune checkpoint inhibitors triggers an oligoclonal expansion of tumor-infiltrating CD8 + T cells that can identify tumor neoantigens generated due to tumor nonsynonymous mutations. This theory has been validated in clinical trials.

3.2. Anti PD 1 inhibitors

Immunomodulation targeting PD-1 is of great significance in anti-tumor, anti-infection, anti-autoimmune diseases and survival of organ transplantation. Its ligand, PD-L1, also serves as a target, and the corresponding antibody can play the same role. Anti-PD 1 inhibitors are a class of new drugs that block PD-1, which can activate the immune system to attack tumors, and are used to treat certain types of cancer, which can inhibit PD 1 and PD-L1. The interaction allows the T cells to attack the target. It is mainly used in the treatment of melanoma and non-small cell lung cancer, and its efficacy in renal cell cancer, bladder cancer, Hodgkin's lymphoma and others is still in large-scale clinical trials. The PD-1 inhibitors such as trelizumab, It is a humanized IgG4-resistant death receptor-1 (PD-1) monoclonal antibody, Trelizumab injection was uniquely modified in the Fc segment of the antibody, Reduced binding effects to Fc R on the surface of macrophages, Thus eliminating antibody-dependent cell-mediated phagocytosis (ADCP), Avoid the impact of the reduced number of effect-tumor T cells; Sintilizumab injection (Sintilimab Injection), by binding to PD-1 and blocking the binding of PD-1 to PD-L1 and PD-L2, Disarm the immunosuppressive effects, Activating the T cell function, Enhance the immune surveillance and killing ability of T cells to treat tumors, Generate a tumor-based immune response. Representative drugs include Nivolumab (Opdivo-Bristol-Myers Squibb, targeting PD-1), Pembrolizumab (Keytruda, MK-3475, Merck, targeting PD-L1), nivolumab, Pan izumab, etc.

4. VEGF

Vascular endothelial abnormal growth factor (VEGF) may be another group of extremely important cellular immunomodulatory factors that regulate the abnormal development of human embryonic stem cells, the abnormal differentiation activity of bone spur growth and other urogenital abnormal tissues, and the normal production and activity of abnormal pathological vascular cells in them. VEGF can help promote the normal and rapid differentiation and growth of human neovascular epithelial cells. When cells and tissues are deprived of oxygenated blood due to impaired circulation, VEGF forms part of the mechanism that restores the blood supply to cells and tissues.

Anti-VEGF strategies for cancer treatment aim to target the pro-angiogenic function of VEGF, thereby inhibiting neointima formation. The direct immunostimulatory effect of VEGF on tumor cells can significantly protect these cells from apoptosis and can increase their resistance to any conventional chemotherapy and radiation therapy [7]. Chemotherapeutic agents and local radiotherapy have been shown to substantially increase the release of free VEGF from implanted tumor stem cells, and this substantial increase in free VEGF production can actually be used to protect implanted tumor cells from these interventions.

The major components of the VEGF family of proteins include VEGF family-protein A, VEGF family-egg B, VEGF family-protein C, VEGF family-protein D, VEGF family-protein E, VEGF family-egg F protein, and PlGF protein. The VEGF family proteins that have not been widely used by scientists in research or use are called VEGF family proteins - egg A. The precursor fragments and mRNA fragments of VEGF-A encoded protein genes can be spliced by variable polarity at the same time and can encode more than eight different protein genes on the expression intervals of VEGF- VEGF-A-encoded proteins located at the expression intervals of more than eight different protein genes denoted as VEGF121, VEGF145, VEGF165, VEGF110, VEGF183, VEGF189, and VEGF209, respectively.

Promote human vascular endothelial cell division and proliferation: VEGF, as a human vascular endothelial cell division factor with specific effects, can significantly stimulate the occurrence of normal vascular endothelial cells located in vitro tissues to carry out the division and proliferation of organic filaments and directional migration, as well as induce the division and formation of abnormal intima in vivo. In the follow-up study of colorectal cancer patients, it was found that VEGF was expressed at a high level and could directly bind to its receptor to promote the mitosis of tumor endothelial cells, thus promoting the normal neovascularization of tumor endothelium [8].

Increase the vascular permeability of small cells: VEGF can effectively and directly increase the normal blood permeability of the vascular endothelial surface of small tumor tissues, especially significantly reducing the abnormal blood permeability of the endothelial membrane of small cells, causing some normal plasma proteins to be leaked by the cells and then transferred to the vascular matrix of the outer surface of the normal vascular membrane, which provides the normal tumor cell vascular endothelium with sufficient blood permeability. It provides important nutrients for the development and rapid maturation of normal tumor endothelium and the rapid establishment of normal capillary meshwork at the site of normal tumor neoplasm.

VEGF receptor protein can induce the production of newly synthesized plasma vascular support receptor protein: VEGF receptor protein can induce the expression of newly synthesized plasma endothelial cells such as urokinase-type fibrinogen-activating factor receptor protein (uPA), tissue protease-activated fibrinogen-activating factor receptor protein (tPA) and urokinase-type fibrinogen-activating factor receptor protein (uPAR) through an effective way. This can effectively promote the formation of new plasma protein clots after the degradation of free plasma proteins that have been infiltrated into the matrix of the extracellular domain of the vascular membrane, and serve as a support for the development and maturation of new vascular tissues.

VEGF is a powerful pro-angiogenic factor, VEGF receptors are usually composed of multiple ligands and multiple receptor clusters superimposed on each other and interlocked, and the receptor proteins and binding arrangements between receptor clusters and at each ligand site have many molecular specificities, and they also have their own specific receptors in various other types of tissue cell matrix networks. The receptors in each ligand site and the binding arrangement also have many molecular specificities, and in various other tissue cell matrix networks they have their own specific receptor cell type characteristics, protein expression regulation level characteristics, and signaling pathway functions. It can simultaneously activate the signaling pathway functions among various other specific VEGFR receptors and eventually form signaling trigger elements and signaling networks. It promotes the biological processes that inhibit the normal cell growth, metastasis, proliferation, and differentiation of normal vascular endothelial cells and normal cell survival and their metabolic activities. In the process of promoting the inhibition of normal tumor cell growth or proliferation and differentiation, the oncogene receptor is activated by mutation, inhibition or oncogene receptor mutated cells undergo a process of mutation activation or cell loss of life after mutation can also often lead to abnormal secretion of large amounts of normal tumor VEGF cells (which can bind to vesicle bodies in endothelial cells). These synergistic controls may include abnormal structural changes in normal cell morphology, other significant changes in cytoskeletal configuration, and direct effects on abnormal endothelial tissue migration and differentiation processes and abnormal normal cell growth. VEGF has been shown to inhibit the expression of vascular endothelial cell genes in several different cell types, which is usually considered to be induced simultaneously or possibly increased to a great extent.

VEGF has been shown to inhibit nuclear factor kappaB (NF κ B) activation in hematopoietic progenitor cells (HPC). Tumor necrosis factor α (TNF α)-mediated activation of I κ B kinase (IKK) and NF κ B was significantly reduced in the presence of VEGF. The effect of VEGF on the apparent inhibition of the NF κ B receptor activation process may be independent of inhibitor VEGFR-1 inhibition and inhibitor VEGFR-2 inhibition since SU5416 is the last inhibitor that effectively inhibits VEGFR-1 inhibition and VEGFR-2 inhibition. NF κ B factor also plays a significant role in the growth of B cells, T cells, and the normal development of dendritic cells. However, the physiological consequences of VEGF-mediated NF κ B inactivation in these cells have not been elucidated [9].

At present, many people have applied monoclonal antibodies, small molecule inhibitors, soluble receptor blocking technology, and other advanced technology methods through targeted drugs to selectively block or change the tumor signal regeneration transduction letter to the pathway or change the depleted tumor vascular cell apoptosis to induce its production of anti-cancer cells VEGF, inhibit the induction of its tumor vascular cell apoptosis generation, to achieve the It can effectively inhibit the growth and abnormal development of tumor necrotic cells and reduce the recurrence of cancer

cells. The main advantage of targeted tumor therapy, which is based on the inhibition of tumor vascular endotheliogenesis imaging as an important therapeutic target, will be mainly reflected in the research of anti-metastatic VEGF drug therapy. Apatinib is a novel oral protein inhibitor known as VEGFR-2, which can effectively inhibit both the resistance to anti-multiply can receptors caused by ABCB1 and in vitro protein rearrangement and pumps-mediated proteins such as ABCBG2/ABCG2, and reverse P-glycoprotein (ABCB1) and breast cancer resistance protein (BCRP) by oral administration, thus reducing the resistance to conventional drugs. resistance to conventional drugs. It also significantly contributes to blocking the abnormal proliferation, migration, and growth of malignant lymphocytes in vivo, and inhibits recurrence and metastasis, while providing essential nutrients for the survival of normal tumor cells in vivo. Therefore, the combination therapy of anti-cancer malignant lymphocytopenia agents can gradually become an important therapeutic anti-tumor technology that has been used in the system of modern clinical anti-tumor drugs and the last drug used in the system of anti-cancer treatment. The use of VEGF-neutralizing antibodies to bind directly to multiple anti-malignant VEGF drug receptors, the use of soluble receptors to bind directly and indirectly to various anti-malignant VEGF drugs, and the use of neutralizing antibodies to multiple anti-malignant VEGFR-3 receptor inhibitors and indirectly or in combination with multiple soluble receptors are all ways of treatment that can produce significant Although the VEGF family is one of the most important types of biochemical factors known to affect functional changes in adult peripheral blood neovascularization and endothelial angiogenesis, it is not the only biochemical factor with a defined function in the adult body, and clinical studies have successfully identified hematopoietic fibroblast growth inhibitors, transforming vascular growth inhibitors, tumor necrosis inhibitors, and tumor necrosis inhibitors. The VEGF gene family members and their immunological relationship with a variety of human and other functional factors for vascular growth of new tissues have yet to be further explored and studied in a systematic and detailed manner. At present, there are nearly 100 kinds of antibody products for VEGF in China, which are in the stage of clinical drug development and experimental application, covering various immunotherapeutic diseases worldwide, including various immune tumors, cancers, visual diseases, and other clinical types of diseases including cardiovascular diseases [10].

5. HER-2

Humanepidermalgrowthfactorre-ceptor-2 (HER-2/C-erbB-2/ErbB-2) is a member of the tyrosine kinase receptor family, which is encoded by the proto-oncogene ERBB2 gene. The receptor tyrosine kinase bound to the cell membrane surface participates in the signaling pathway leading to cell growth and differentiation, which plays an important role in the proliferation and differentiation of normal cells, and is an important regulator of cell proliferation, differentiation and survival. HER-2 has not found specific ligands, which must form a heterodimer with other family members. Other members' ligands activate EGFR, HER-3 or HER-4 kinase and undergo body phosphorylation to activate downstream signaling pathways (such as Ros-RO-Meh-MAPK, PGK-Akt-mTOR, etc.), and then mediate cell ion exchange, gene expression, DNA synthesis and other processes

The entire RAS / MAPK signaling pathway is important as regulators in embryonic development, in biological processes, including cell differentiation, proliferation, and death, and the MAPK family is a major member of this signaling pathway. It includes a series of protein kinase cascade: Ras is activated after binding to GTP, making Raf recruited to the cell membrane and bind to it, then MEK and MAPK are activated in turn, MAPK activates some transcription factors, protein kinases, triggering a variety of biological effects. Alternatively, RAS / GTP can cross MEKK to activate MEK [11].

Phosphatidylinositol-3-ki-nase (PI3K), known because it can phosphorylate 3f_ OH on the phospholipid inositol ring, is a family of many lipid kinases. For example, a class of PI3K (class- - IPI3K) consists of a regulatory subunit (P85) and a catalytic subunit (P110), which can be divided into two categories due to activation by receptor tyrosine kinases or Gone-protein-coupled receptors.

When the corresponding receptor is activated by the ligand, it binds and activates P85, and then P110 is recruited close to the membrane and binds to P85 to form a heterodimer, followed by PI10 activation, catalyzing the phosphoinositol diphosphate (phosphatidylcholine tol (4,5), bisphosphate, PIP₂) on the membrane surface to generate phosphoinositol triphosphate (phosphatidylinositol (3,4,5) trisphosphate, PIP₃). PIP₃, as a second messenger, positioning Akt and phosphatidylinositol-dependent kinase1 (PDK1) to the inner surface of the membrane through their respective PH domains. PK phosphorylate Thr308 residues of Akt, in addition, PK phosphorylate Ser473 residues at AktC terminals in a similar manner, so Akt is fully activated, acting on multiple substrates to regulate cell survival, proliferation and metabolism of [12].

HER-2 can indirectly regulate the expression of many tumor-related genes through the signal transduction pathway, or directly act as transcription factors for certain gene expression, and some gene expression products can further enhance the expression of HER-2 or other genes, which constitutes a gene expression regulation network centered on HER-2, which may become the markers of tumor diagnosis and prognosis [13]. Under normal circumstances, the gene is in a non-activated state and participates in the regulation of cell differentiation. When affected by factors in vitro and in vivo, its structure or expression regulation is abnormal, and thus it is activated with neoplastic transformation activity. It has been established that the oncogenicity of the HER-2 gene is through the amplification of this gene and the high expression of the protein. Mutational events with low frequency of HER-2 signal transduction complexes, including small insertions, missense mutations in different regions, or large deletions, etc. When the above changes occur, the downstream cascade of HER-2 signal is abnormally activated, and the product P45 itself phosphorylates other substrates, eventually leading to cell proliferation and cancerous [14]. In vitro experiments found that HER-2 overexpression can lead to malignant transformation of non-tumor cells and breast cancer J in transgenic mice, and have different degrees of amplification and overexpression of in various tissue tumors such as human breast, lung, ovarian, gastric and colon cancer [15].

Activation of HER2 causes a phosphorylation cascade of its downstream molecules, Activation of Proactivation protein kinases (mitogen activated protein kinase, MAPK), phosphatidylinositol-3-kinase-protein kinase B / Akt (phosphatidylinositol 3'-kinase-protein kinase B / Akt, PI3K-PKB / Akt), phospholipase C-protein kinase C (phospholipase C-protein kinase C, PLC-PKC) and transcriptional signaling and activation proteins (signal transducers and activators of transcription, STAT), and many other major signaling pathways. A large number of experimental studies show that, HER2-mediated signaling can regulate the expression of tumor-related genes, Such as the up-regulation of the vascular endothelial (cell) growth factor (vascular endothelial growth factor, VEGF), urokinase-type plasmin activator (urokinase-type plasminogen activator), Cyclooxygenase-2 (cyclooxygenase-2, COX-2), the chemotactic cytokine receptor CXCR-4 expression, Downregulation of the MMP repressor RECK expression. HER2 overexpression can activate AKT and nuclear factor-KB (NF-kB), and continuously activated AKT and NF-kB can lead to anti-apoptotic cascade, make cancer cells resistant to TNF- α and reduce host defense against tumors. Thus, it promotes tumor ridge invasion and metastasis.

Pertuzumab is a human monoclonal IgG1 antibody that acts on the extracellular receptor domain II (dimer region) J of the HER-2 receptors. By targeting to this site, specifically inhibit HER-2 homodimer or heterodimerization with HER1, HER3 and HER4, thereby blocking HER-2 receptor activation and inhibiting associated tumor cell growth dependent upon HER-2 receptor activation.

6. Conclusion

In This paper, the previous drug mechanism of action is analyzed, and the advantages and disadvantages of various drugs are also reflected. However, with the improvement of drug resistance of cancer cells and the development of diffusion, we should strengthen the cognition of the target mechanism and bring forth the new. Although the several targeted drugs mentioned above are all powerful tools against cancer in recent years, these drugs have been born through an extremely long

development cycle and continuous trial and error, and the updated iteration of drugs needs our sincere research. However, it is worthwhile to conduct research, where to focus more on the research direction, and whether there is a better solution to the cancer. In this study, we found that the protein direction is an important breakthrough, hoping to have the opportunity for further research and exploration. As far as the current research and promotion of malignant tumors is concerned, first of all, it is necessary to continuously advance on the road of cancer-related life science. It is necessary to find out better targets, find out the targeted drugs with better effects, and reduce the harm of side effects with greater effectiveness.

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