Research on Cervical Cancer and Its Drug Treatment

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Abstract. Cervical cancer is one of the common malignant tumors in gynecology, usually due to persistent infection with human papillomavirus (HPV). At present, the main therapeutic drugs used in clinical practice are traditional chemotherapeutic drugs and targeted drugs, and drug therapy mainly includes traditional cytotoxic chemotherapy, targeted therapy, immunotherapy. Because traditional chemotherapeutic drugs usually can not solve the problem of drug resistance and side effects, people started using molecular biology and genomics study of targeted drug therapy. This article mainly discusses the target drug treatment of cervical cancer, anti-angiogenesis, immune checkpoint inhibitor treatment methods, as they have been applied in the treatment of cervical cancer and showed effect, which also brought new hope for the treatment of cervical cancer.

1 Introduction

Cervical cancer is one of the common malignant tumors among women, and the incidence rate is only secondary to breast cancer. At present, more than 460,000 new cases of cervical cancer occur annually worldwide[1]. More than 130,000 new cases are added to China annually, accounting for more than 28% of global cases. At the same time, clinical cases show that the incidence of cervical cancer in recent years presents regional growth and early onset of age and other characteristics. Because cervical cancer poses a major threat to women's health, research on the treatment of cervical cancer has always been the focus of public attention. This article will discuss the pathogenesis of cervical cancer, drug treatment plan and its defects, and new strategies of drug treatment. The author hopes to bring some advice to the treatment of cervical cancer, so that people can understand and pay more attention to this disease.

2 Human papillomavirus and cervical cancer

The discovery that cervical cancer is mainly caused by persistent infection with high-risk human papillomavirus (HPV) found by German scientists Harald zur Hause has made cervical cancer the only cancer with a clear etiology and won the 2008 Nobel Prize in physiology and medicine. HPV, a small, membrane-free DNA virus, has identified more than 150 HPV viruses, of which high-risk HPV 16 and HPV 18 can cause about 70% of cervical cancer[2].

2.1 HPV genome structure and function of its encoded protein

HPV genome can be divided into three functional areas, including early transcriptional regions (E regions), late transcriptional regions (L regions), and upstream regulatory regions (URR regions). E District Governor bp, approximately 4,500 encoding early protein E1, E2, E4, E5, E6 and E7, is involving in regulating the life cycle of the virus and regulating DNA replication, transcription, and translation of viral proteins[3]. E6 and E7 are the major carcinogens, and E6 is a small molecule protein without enzyme activity. The relative molecular mass (Mr) was (16~18)×103. While E7 is a cell cycle regulator, containing 98 amino acids, and its Mr is about 12×103. L District Chief bp, approximately 3,000 encoding late protein L1 and L2, is the capsid protein of the virus, involved in the process of cell surface adsorption, virus particle packaging and virus entry into the cytoplasm. URR region contains cis regulatory units and the starting point for viral replication, which is responsible for regulating the replication and transcription of viral genetic materials. The following figure 1 shows the genome structure of HPV16.

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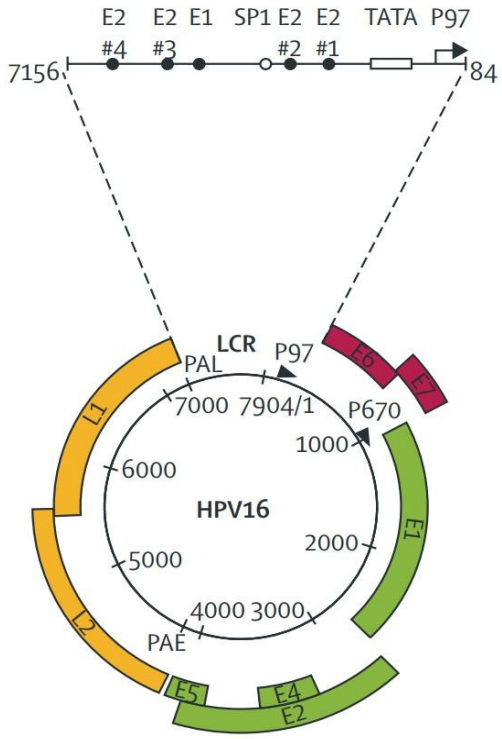

Fig. 1. Genome structure of HPV16

2.2 HPV carcinogenic mechanisms

The expression of high-risk E6/E7 proteins in cells is key to infection HPV initiation of cell carcinogenesis. One of the most important roles of E6 proteins is the ubiquitination and degradation of p53 proteins[4]. P53 protein is an important tumor suppressor, which can promote apoptosis, block cell cycle and inhibit tumor angiogenesis. There are several p53 protein binding sites on the E6 protein. After forming the E6-E6-AP complex with the ubiquitin ligase, the p53 protein can be recruited and ubiquitinated. Ubiquitin enzyme promotes the degradation of p53 through the proteasome, making the p53 protein lose its normal function, thus inhibiting apoptosis and causing tumorigenesis[5]. The figure 2 below shows the effect of high-risk HPV on the cell cycle.

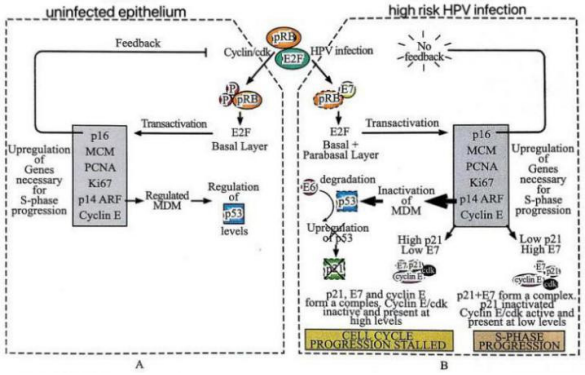

Fig. 2. Effect of high-risk HPV on cell cycle

3 Target Drug Therapy for Cervical Cancer

At present, the clinical treatment of cervical cancer mainly includes surgical treatment, radiotherapy and chemotherapy. The traditional view is that cervical cancer is insensitive to chemotherapeutic drugs. Therefore, the surgery and radiotherapy are usually the treatment methods. However, with the deepening of research, a large number of experimental results and clinical practice have confirmed that surgery and radiotherapy can not completely control or eliminate the occurrence and metastasis of cervical cancer. With the replacement of chemotherapeutic drugs and the improvement of methods, as well as ways of drug delivery, drug target therapy has gradually become an important means of cervical cancer treatment.

In recent years, several gene mutations have been found in cervical cancer tissues through different methods, and these mutations may contain the driving genes that cause tumorigenesis and development, which may become an effective target for antitumor therapy.

3.1 Antiangiogenic therapy

Vascular endothelial growth factor (VEGF) is highly expressed in many tumors, including cervical cancer, whereas bevacizumab is a VEGF monoclonal antibody. In addition to inhibiting neovascularization, reducing tumor blood supply and inhibiting tumor growth, bevacizumab can also improve the disorder of tumor vessels, make chemotherapeutic drugs enter the tumor more easily, and increase the sensitivity of the tumor to chemotherapy[6]. Clinical studies have shown that bevacizumab improves the prognosis of patients with recurrent and metastatic cervical cancer, and that bevacizumab combined with chemotherapy significantly improves overall survival (OS)[7].

3.2 Epidermal growth factor receptor (EGFR) family inhibitor

EGFR family is associated with cell proliferation, differentiation, and regulates tumorigenesis, growth, and invasion. Human papillomavirus type 16, E6 and E7 proteins in cervical cancer cells can stimulate the expression of EGFR in cervical cancer epithelial cells. 40%~80% of cervical squamous cell carcinoma are expressed. High expression of cervical cancer has high tumor grade and poor prognosis, and is associated with chemoradiotherapy resistance[8]. However, studies have shown that EGFR monoclonal antibody Cetuximab alone or in combination with chemotherapy has no significant survival benefits in the treatment of recurrent or residual cervical cancer, with large adverse reactions. Therefore, EGFR family inhibitors still need to be further studied.

3.3 Immune checkpoint inhibitors

T lymphocytes are important effector cells that mediate tumor immune response. T cell activation requires T cell

receptor-mediated antigen-specific signals and costimulatory molecule-mediated costimulatory signals. Programmed death ligand-1 is a newly discovered negative synergistic stimulatory molecule that negatively regulates tumor immune response by binding to programmed cell death-1 and inhibiting T cell activation and proliferation. It also plays an crucial role in the immune escape mechanism of tumor cells[9]. Programmed death ligand-1 is also known as the immune checkpoint. The expression rate of programmed death ligand 1 in cervical intraepithelial neoplasia cells is 95%, compared with 80% in cervical squamous cell carcinoma. High levels of programmed death ligand-1 positive antigen-presenting cells and regulatory T cells are found in metastatic lymph nodes. The above data indicate that immune checkpoint inhibitors have great potential in the treatment of cervical cancer. The following figure 3 shows the effect of immunosuppressants on cancer cells.

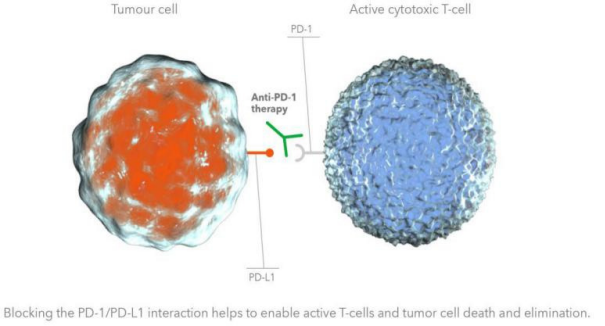

Fig. 3. Effects of immunosuppressive agents on cancer cells

4 Discussion

Molecular targeted therapy (molecular target therapy, MTT) is the control of cell gene expression through signal transduction pathways that specifically target molecules or related cells, which play key roles in tumorigenesis and development, thereby inhibiting or killing cancer cells. Based on the signal transduction mechanism, tumor cells at the molecular level precision can lead to cervical cancer link directly or indirectly. This can be from molecular level to reverse the malignant biological behavior, thus inhibiting tumor cell growth, and even make them completely subsided. This maybe become a new biological treatment mode. Molecular targeted therapy mainly includes anti-angiogenic drugs, tyrosine kinase inhibitors and epidermal growth factor receptor blockers, among which some drugs combined with chemotherapy have become the first-line treatment for recurrent or metastatic cervical cancer. But with the widespread adoption of cisplatin-based chemoradiotherapy in locally advanced diseases, concerns have been expressed about platinum resistance and radiation resistance at recurrence, which has prompted us to develop new targeted drugs. Since E6 and E7 are drivers of tumor progression, numerous basic studies and clinical trials have targeted E6/E7 genes to find effective treatments for cervical cancer.

The first targeted therapy is antiangiogenic therapy, which uses monoclonal antibodies of vascular endothelial growth factor such as bevacizumab to inhibit neovascularization. It can cause insufficient blood supply to tumor cells and inhibit their growth. It can also increase the sensitivity of the tumor to chemotherapy, which is the best practical targeted therapy method at present in the author's eyes. The second targeted therapy is to inhibit the expression of cervical cancer epithelial cells and slow down the rate of tumorigenesis by using the monoclonal antibody Cetuximab, a family inhibitor of epidermal growth factor receptor. However, the adverse reactions are large, so this method still needs to be studied and optimized. The third targeted therapy is to use the combination of programmed death ligand-1 and programmed death-1 to inhibit the activation and proliferation of T cells and negatively regulate the tumor immune response. This approach may have the greatest future potential because it uses the body's own T lymphocytes to regulate tumor cells.

Now that cervical cancer is becoming more common, which is more evident of the importance of HPV vaccine, the author thinks the world should pay attention to this disease and take it as one of the vaccines that must be injected. Three types of prophylactic HPV vaccines have been marketed in many countries around the world and can be used to prevent HPV-related diseases. Among them, GSK 2, MSD 4 and 9 HPV vaccines can prevent more than 90% of cervical cancer.

5 Conclusion

Currently, drug therapy is an important part of cervical cancer treatment, but targeted therapy provides a new direction for the treatment of cervical cancer, in which bevacizumab combined with chemotherapy can improve the survival of patients with recurrent metastatic cervical cancer. Preliminary studies have demonstrated the application prospect of immune checkpoint inhibitors in the treatment of cervical cancer, and further research is still needed for further exploration. In addition, new molecular targeted drugs in the field of cervical cancer application research is also being carried out, and these studies will provide new ideas and basis for the treatment of cervical cancer drugs.

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