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Research Progress on the Correlation between PTEN and Tumors

Xiaohui Cui[1,2], Shufeng Du[1,2], Rongrong Li[1,2], Xiaoxia Jiang[1,2], Taihua Wang[1,2,*]

[1]Shandong New Medicine Research Institute of Integrated Traditional and Western Medicine, Jinan, Shandong Province, 250101
[2]Interventional Hospital of Shandong Red Cross Society, Jinan, Shandong Province, 250101
*Corresponding author: ganxibaowangtaihua@163.com

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Abstract PTEN is a tumor suppressor gene with dual specific phosphatase activity discovered after p53. and its deletion and mutation are closely related to the occurrence of a variety of malignant tumors. PTEN regulates cell proliferation, survival, and metabolism by inhibiting the activity of the PI3K/Akt signaling pathway, many components of which have been found to be involved in tumorigenesis. Although the mechanisms by which PTEN function is disrupted are diverse, the most frequently observed events are deletion of a single gene copy of PTEN. In this paper, the data relating to PTEN loss in some common tumour types and the related treatment of tumors are reviewed.

Keywords: *PTEN, PI3K/Akt, tumorigenesis, treatment*

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1. Introduction

In recent years, the incidence of malignant tumors and the mortality of patients have increased year by year, which has seriously threatened human health. As a tumor suppressor gene, PTEN plays a key role in maintaining the stability of the genome and preventing tumors. In recent years, it has been recognized as one of the most frequently mutated genes in human tumors [1]. The PTEN gene was discovered on human chromosome 10 by three independent research teams in the United States in 1997. At the same time, the gene is frequently deleted in brain, prostate and bladder cancers [2,3]. Subsequently, mutations in the PTEN gene were also found in the germ cells of a group of patients with autosomal dominant syndrome. This disease is collectively referred to as PTEN hamartoma tumor syndrome (PHTS), which is characterized by multiple hamartomas and cancer susceptibility increase. PTEN has the function of phosphorylase, as a negative regulator of phosphoinositide-3 kinase (PI3-K)/ser-threonine kinase (AKT) pathway, PTEN/PI3K/Akt pathway plays an important role in the response of cells to integrate external stimuli. At its core, the lack of PTEN function is closely related to the occurrence of tumors. The protein encoded by PTEN can finely regulate the level of protein phosphorylation in cells, thereby affecting cell growth, proliferation, differentiation, apoptosis, adhesion and migration. PTEN gene has attracted much attention for its unique pathway of action and its important role in the pathogenesis of a variety of human tumors.

2. Correlation between PTEN and Tumors

The PTEN gene was first described in 1997 as a gene that prevents the cell cycle to the G0-G1 phase and eventually leads to apoptosis [4]. The PTEN gene contains 9 exons and 8 introns [5], which encodes a 47 kD protein containing 403 amino acids. The protein has dual specific activities of lipid phosphatase and protein phosphatase, and is involved in the regulation of cellular Physiological processes such as growth, apoptosis and signal transduction pathways [6]. PTEN belongs to the family of protein tyrosine phosphatases and has the effect of antagonizing the phosphorylation of peptides and phosphoinositol substrates [7]. The PTEN protein contains an N-terminal phosphatase catalytic domain and a C-terminal lipid-binding C2 domain (residues 186-351) [8,9,10,11]. The N-terminal domain has dual specificity phosphatase-like enzyme activity, and the C-terminal C2 domain can selectively bind to the membrane in vitro and dephosphorylate PIP3 [9,10,12]. These domains play a vital role in maintaining the biological activity of lipid phosphatase [10].

PTEN is an effective tumor suppressor gene, and loss of its function is often observed in inherited and sporadic cancers. The PTEN gene can affect its target protein and its downstream signaling cascade, and play an important role in the negative regulation of multiple signaling pathways. A small decrease in the level and activity of PTEN protein may lead to an increase in cancer susceptibility and tumor malignancy. Experiments in

gene-deleted mice proved that PTEN has an inhibitory effect in a variety of tumor types [13,14,15]. In terms of genetic analysis, PTEN is manifested as haploid deficiency in some cancerous tissues [16]. In addition, studies on human samples and PTEN hypogenic mice have shown that even partial loss of PTEN function is sufficient to promote the occurrence of certain types of cancer, and PTEN levels below 50% will further accelerate the progression of cancer. Consistent with the profound effect of PTEN on the fine down-regulation of tumor development, it is often found in cancer that too many mechanisms regulating PTEN expression and function have been altered. In addition to mutations, PTEN gene expression inhibition or PTEN subcellular localization abnormalities lead to functional inhibition that is closely related to tumor occurrence and disease progression [17].

3. The Regulatory Mechanism of PTEN and Tumors

3.1. PTEN/PI3K/AKT Signal Pathway

PTEN/PI3K/AKT is an important signal pathway that regulates a variety of biological processes such as apoptosis, metabolism, cell proliferation, and growth. The PI3Ks family of lipid kinases is composed of three different subtypes of PI3K (Class I, Class II, and Class III). Each PI3K subtype is based on its different structural characteristics, effects on specific substrates, and basic principles of activation. Cell growth, survival, proliferation, differentiation, cell migration and other aspects play a specific role [18]. As a lipid phosphatase, PTEN negatively regulates the phosphatidylinositol 3-kinase (PI3K) signaling cascade, thereby inhibiting the downstream protein kinase B (PKB/AKT) signaling pathway [19,20]. Under the stimulation of growth factors, PI3K is activated and catalyzes the phosphorylation of PIP2 to PIP3. PIP3 recruits PDK1 to the plasma membrane and promotes the activation of AKT. AKT regulates a large number of downstream cell processes, such as cell growth, proliferation, and reduction of apoptosis. The lipid phosphatase activity of PTEN counteracts the effect of PI3K by dephosphorylating PIP3 to PIP2, thereby inhibiting the activation of AKT. Once the PTEN gene is mutated or deleted, resulting in abnormal or obstructed protein synthesis, the expression level of PTEN protein is reduced, and the dephosphorylation of PIP3 into PIP2 is weakened, so that PIP3 accumulates excessively in the cell, which will inevitably lead to PI3K/Akt conduction. The pathway continues to be in an activated state, which eventually leads to the loss of control of cell proliferation or apoptosis, triggering a series of diseases [21,22].

3.2. RAS and PI3K Signal Pathway

Activation of mutation points in the coding region of the GTP binding protein subfamily Ras gene contributes to the formation of most human tumors [23]. The expression of active Ras protein promotes tumor initiation by activating at least three different effectors such as Raf, PI3K, and RalGEFs [24]. Raf is a serine/threonine kinase that is located in the plasma membrane of the cytoplasm and is activated by GTP-Ras. The activated Raf protein then initiates the MAP kinase (MAPK) signal transduction cascade, leading to cell transformation and non-anchoring sexual growth and promotion of angiogenesis [25]. Finally, the RalGEFs family of guanine exchange factors are activated by the recruitment of GTP on the plasma membrane. According to reports, the Ras effector pathways MAPK, RalGEF and PI3K are necessary conditions for tumor growth in human cells [26,27,28]. On the contrary, when the tumor is formed, the activation of the PI3K/AKT pathway replaces the activation of the Ras protein, but there are other Ras effectors that are still activated independently, which may be determined by the factors provided when the tumor microenvironment is established. Therefore, with the progression of tumorigenesis, at least in the case of Ras, the dependence of cancer on its initiating oncogene is reduced to the PI3K/AKT pathway [28].

4. PTEN Deficiency and Tumors

4.1. PTEN Deletion and Malignant Glioma

The frequent mutations of PTEN found in malignant gliomas provide key data for the discovery of tumor suppressors [1,2] and promote in-depth research on the role of PTEN deletion in the occurrence of fatal tumors. Almost all malignant gliomas show loss of PTEN tumor suppressor function. Data from the Cancer Genome Atlas shows that, including the deletion of PTEN at 143/170 (85%) in malignant gliomas, PTEN gene deletion is the most common genetic change found in cancer, which is in line with the recognized PTEN. The multiple mechanisms of loss of function in cancer are consistent. Mutations in the PTEN coding sequence often occur in malignant gliomas. About 30% of malignant gliomas are often accompanied by the loss of the second allele of the entire coding sequence of PTEN, which in turn affects the regulation and catalytic function of pTEN [29,30]. Correspondingly, immunohistochemical detection of most cancers found that most of the PTEN protein will be lost [31,32].

4.2. PTEN Deletion and Breast Cancer

Breast cancer is the most common malignant tumor and the main cause of cancer death in women worldwide. Breast cancer is a heterogeneous disease, which can be divided into different subtypes. Each subtype shows different clinical and pathological characteristics and shows different treatment responses. A number of studies have shown that PTEN loss is closely related to the occurrence and development of various subtypes of breast cancer [33]. Immunohistochemical analysis of patient-derived samples found that 40% of primary breast cancers had lost or decreased PTEN protein expression. The prognostic value of PTEN loss in breast cancer has been intensively studied. For example, the analysis of the results of 27 studies and the data of 10231 cases of breast cancer shows that the absence of PTEN has a great

correlation with the malignancy of the tumor [34]. The malignancy of the tumor is determined by several clinical factors such as tumor size, lymph node metastasis, and cell differentiation. Pathological parameters were analyzed and evaluated. The results of multiple studies have shown that PTEN methylation plays an important role in the pathogenesis of breast cancer. The methylation of the CpG islands in the promoter region of the PTEN gene will affect gene expression, and the higher the degree of methylation, the lower the gene expression will decrease, or even no expression. Stefansson's research shows that breast cancer patients with hypermethylation of CpG sites often have a poor prognosis [34]. There are also trials that have found that PTEN gene methylation exists in a considerable proportion of patients with lymph node metastasis and breast malignant tumors [35]. These studies all suggest that PTEN gene methylation is closely related to the development of breast cancer.

4.3. PTEN Deficiency and Endometrial Cancer

Endometrial cancer is the most common malignant tumor of the female reproductive tract and the fifth most common cancer affecting women worldwide. According to different histology and clinical results, endometrial cancer is traditionally divided into two main categories. The first category is also called endometrioid endometrial carcinoma (EECA), which accounts for the majority (70-80%). It occurs in pre- and perimenopausal women and is related to estrogen exposure. Clinically, it is mainly low grade, and the overall prognosis is good. In contrast, the second type of endometrial cancer is usually a high-grade serous carcinoma or a lower-grade clear cell tumor. This type has nothing to do with estrogen and is characterized by a low degree of cell differentiation. Compared with the first type of endometrial cancer, the second type of endometrial cancer has a poor prognosis, and has a relatively low incidence (10-20% of all endometrial cancers) and a high mortality rate (about 40%).

PTEN is the most common mutated gene in endometrial cancer, and the endometrioid subtype has the highest percentage of PTEN coding sequence variation in all types of tumors [36]. In contrast, mutations in the PTEN gene are very rare in the second type of serous carcinoma [37]. In terms of clinical significance, the loss of PTEN function in the endometrium has been assumed to be an early parameter of canceration at this site, and it is also closely related to a good prognosis. Higher frequency PTEN mutations are usually found in pre-malignant lesions, a type of late-stage tumors, or metastatic diseases.

4.4. PTEN Deficiency and Ovarian Cancer

According to invasive epithelial ovarian cancer, it is divided into low-grade and high-grade. There are usually four histological subtypes: serous type, endometrioid, mucous type and clear cell type. PTEN mutations are rare in ovarian cancer and are mainly found in studies of endometrioid subtypes. One or two coding regions of PTEN are often lost in endometrioid, clear cell, and high-grade serous ovarian cancer [38]. Immunohistochemical analysis of multiple ovarian cancers showed that the expression level of PTEN frequently decreased, which was consistent with the level of loss of PTEN copy number. Another study showed that PTEN loss of heterozygosity was found during the transformation of endometriosis to endometrioid ovarian cancer[39]. Combined analysis of genetics and immunohistochemistry shows that, like many cancers, many tumors retain at least one copy of the wild-type PTEN gene, but do not show detectable PTEN protein.

4.5. PTEN Deficiency and Lung Cancer

Lung cancer is the cancer with the highest mortality rate in the world, and the 5-year survival rate of patients is only about 15%. Lung cancer is histologically divided into two subtypes, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLCs), and then further divided into three subtypes based on histological characteristics: adenocarcinoma (the most common is ADC), squamous cell carcinoma (SCC) and large cell carcinoma (LCC) [40]. Immunohistochemical analysis of PTEN expression in NSCLC showed that about 30-50% of NSCLC have tumor suppressor protein loss. The loss of PTEN function in NSCLCs is very small in adenocarcinoma compared with other forms of non-small cell lung cancer.

4.6. PTEN Deletion and Prostate Cancer

In 1995, a study by Gray et al. found that 62% of prostate cancers have the loss of the q23-24 region on chromosome 10. Subsequently, the PTEN gene was discovered through the study of these missing prostate cancer samples [1,2]. Research on the frequency of PTEN mutations in prostate cancer has reached the same result through a variety of technical methods. In prostate cancer, the most common occurrence of PTEN is a copy number change rather than a point mutation [41]. Missense mutations or nonsense mutations are usually found in 5% of primary prostate cancers, but the possibility of such mutations in metastatic cancers is relatively high. On the other hand, when there is a point mutation, it is often found that the point mutation is combined with the deletion of the second PTEN allele, which ultimately leads to the loss of homozygous function [41]. In addition, studies have found that the incidence of PTEN deletion in metastatic prostate tumors is higher than that of primary prostate tumors, and their occurrence probability is between 30-45% and 10-20%, respectively [42]. The function of PTEN is regulated at the pre-transcriptional, post-transcriptional and translational levels, and changes in each step of the process may lead to the occurrence of prostate cancer.

4.7. PTEN deletion and Colorectal Cancer (CRC)

Colorectal cancer, also known as colorectal cancer, is the third most common cancer in the world, with approximately 1.3 million newly diagnosed cases each year. The loss of function of the tumor suppressor gene PTEN is one of the most common causes of sporadic colorectal cancer. Similar to several other cancers, the

main change of PTEN gene in colorectal cancer is also the loss of copy number. PTEN protein is found to be missing in most colorectal cancers. This phenomenon is closely related to the loss of PTEN gene copy number. Although the PTEN gene deletion level is high, the mutation/focal deletion rate of PTEN in CRC is usually relatively low. For example, a cancer genome atlas study found a 4% focal deletion rate and a single PTEN mutation in 165 samples [43]. However, there are also studies that have found high PTEN mutations in 9%-20% of colorectal cancers [44]. Considering that PTEN mutations tend to increase with the severity of CRC disease, the analyzed tumor stage can explain some of these differences.

5. PTEN Gene and Tumors Targeted Therapy

The PTEN/PI3K/AKT signaling pathway is closely related to the occurrence and development of tumors. Any protein in this pathway is a potential target for cancer treatment. Many companies and laboratories have begun to adopt various methods to inhibit this approach at different points to explore. PI3Ks, PDK1, AKT and mTOR are all important targets for different treatment methods. Many studies have shown that inhibition of the PI3K pathway can increase the sensitivity of chemotherapy to several cytotoxic therapies and other non-PI3K pathway-guided inhibitors [45]. However, inhibiting the PI3K pathway may produce undesirable side effects, such as hyperglycemia.

In recent years, molecular target therapy has become a hot spot in tumor treatment. In view of the important role of PTEN in tumorigenesis and development, treatment strategies targeting PTEN have emerged one after another. Various in vivo and in vitro experiments have confirmed that PTEN has an inhibitory effect on the occurrence and development of tumors. Wild-type PTEN gene replacement therapy is the basic method of tumor suppressor gene therapy. The main method is to introduce wild-type PTEN gene into the genome of malignant tumors through transgenic technology, and replace the mutant PTEN gene in tumor cells to perform normal functions. Davies [46] introduced Ad-PTEN into prostate cancer cells and found that the expression of PTEN gene transferred in vitro could not inhibit the tumorigenicity of the cells, but it could significantly reduce the tumor size and completely inhibit tumor metastasis; and lead to human tumor cells in vivo. After that, there was no significant reduction in the size of the local tumor, but the probability of metastasis was reduced. The above research results indicate that Ad-PTEN gene expression can inhibit the proliferation and metastasis of prostate cells.

In the method of treating tumors, the combination therapy of PTEN is also involved. Studies have confirmed that the occurrence and development of tumors is a complex process involving multiple genes and multiple factors. Scholars at home and abroad have found that PTEN gene and certain therapeutic factors have a synergistic effect on tumor gene therapy, and the efficacy is better than single-factor therapy. Tanaka et al. [47] introduced Ad-PTEN into PC-3 cells and injected doxorubicin, and compared it with PTEN gene or doxorubicin and other single-factor therapies, and found that the efficacy of combination therapy was significantly higher than that of single-factor therapy. Rosser et al. [48] introduced Ad-PTEN into prostate cancer cells before radiotherapy and found that the survival rate of prostate cancer cells expressing bc1-2 decreased from 60.55 to 3.6%, while the survival rate of other cell lines did not decrease significantly or did not decrease. . It shows that Ad-PTEN can increase the sensitivity of prostate cancer cells expressing bcl-2 to radiation.

6. Prospect

The research of tumor molecular biology has promoted the development of anti-tumor compound targeting research. In this new approach to the discovery process of new drugs, the choice of molecular targets has become the most important issue. The mechanism of PTEN gene and its related signaling pathways has become a hot spot in targeted research. Further research on the PTEN gene signaling pathway will also provide more new ideas and basis for the diagnosis and treatment of tumors at the gene level.

Conflict of Interest Statement

The authors report no conflicts of interest.

Ethics Statement

Since this manuscript is a systemic review of the implication of PTEN in tumors, it was not needed for approval from the ethics committee or institutional review board.

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