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Progress in the correlation between PTPN12 gene expression and human tumors

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Abstract

Background: The global morbidity of cancer is rising rapidly. Despite advances in molecular biology, immunology, and cytotoxic and immune-anticancer therapies, cancer remains a major cause of death worldwide. Protein tyrosine phosphatase non-receptor type 12 (PTPN12) is a new member of the cytoplasmic protein tyrosine phosphatase family, isolated from a cDNA library of adult colon tissue. Thus far, no studies have reviewed the correlation between PTPN12 gene expression and human tumors.

Methods: This article summarizes the latest domestic and international research developments on how the expression of PTPN12 relates to human tumors. The extensive search in Web of Science and PubMed with the keywords including PTPN12, tumor, renal cell carcinoma, proto-oncogenes, tumor suppressor genes was undertaken.

Results: More and more studies have shown that a tumor is essentially a genetic disease, arising from a broken antagonistic function between proto-oncogenes and tumor suppressor genes. When their antagonistic effect is out of balance, it may cause uncontrolled growth of cells and lead to the occurrence of tumors. PTPN12 is a tumor suppressor gene, so inhibiting its activity will lead directly or indirectly to the occurrence of tumors.

Conclusion: The etiology, prevention, and treatment of tumors have become the focus of research around the world. PTPN12 is a tumor suppressor gene. In the future, PTPN12 might serve as a novel molecular marker to benefit patients, and even the development of tumor suppressor gene activation agents can form a practical research direction.

Abbreviations: CRC = colorectal cancer, EGFR = epidermal growth factor receptor, HCC = hepatocellular carcinoma, IHC = immunohistochemistry, NSCLC = non-small cell lung cancer cells, PTP = protein tyrosine phosphatase, PTPN12 = protein tyrosine phosphatase non-receptor type 12, PTP-PEST = protein tyrosine phosphatase, STAT3 = signal transducer and activator of transcription 3, VCP = valin-containing protein.

Keywords: proto-oncogenes, protein tyrosine phosphatase non-receptor type 12, renal cell carcinoma, tumor, tumor suppressor genes

1. Introduction

In recent years, tumors have become 1 of the major causes of human death.[1] With the rapid development of molecular biology, tumor molecular epidemiology came into being. Through the study of the etiology and pathogenesis of tumors, researchers aim to prevent and treat human tumors more effectively. The etiology and pathogenesis of some tumors have been gradually revealed. More and more studies have shown that the essence of tumors are genetic diseases.[2,3] The growth and proliferation of cells are mainly regulated by 2 types of signals.

One type of signal is designed to promote the proliferation and growth of human cells and inhibit the differentiation of tissues.

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Most proto-oncogenes play an important role in this process of malignant tumor growth. They can also be integrated with the host cell genome through transcription, leading to the occurrence of cancer.[4] The oncogenic effects of proto-oncogenes must be activated to achieve this task.[5]

Another type of signal is mainly involved in inhibiting cell proliferation, promoting tissue differentiation, maturation and aging, or apoptosis. Tumor suppressor genes play an important role in this process.[6–8] In the future, they may even become an indispensable method for tumor treatment.[9] A lot of research has been done on tumor suppressor genes.[10] These genes are present in normal cells, but once the tumor suppressor function is lost, it can lead to the occurrence of tumors.[11,12]

Environmental factors and genetic carcinogenic factors may lead to gene mutation in cells, changing both apoptosis-regulating genes and DNA repair genes. These mutations may result in the inactivation of tumor suppressor genes and the activation of proto-oncogenes, which may change the growth pattern of cells. The mutation of proto-oncogenes is dominant; however, the mutation of tumor suppressor genes is recessive. The mutation of apoptosis-regulating genes can appear as either dominant or recessive.[13] The mutated cells may first show polyclonal hyperplasia and in the course of its evolution, there may be relatively unlimited monoclonal hyperplasia. Through additional mutation, subclonal proliferation of monoclonal hyperplasia occurs, leading to infinite proliferation of cells with different characteristics. These cells gradually gain the ability to infiltrate and metastasize, transforming cells to malignant masses and eventually leading to the occurrence of malignant tumors.[14]

2. Methods

This article summarizes the latest domestic and international research developments on how the expression of protein tyrosine phosphatase (PTP) non-receptor type 12 (PTPN12) relates to human tumors. The extensive search in Web of Science and PubMed with the keywords including PTPN12, tumor, renal cell carcinoma, proto-oncogenes, tumor suppressor genes was undertaken.

3. Results

3.1. Function of the PTPN12 gene

Using PCR products as probes, Takekawa et al cloned and identified PTPN12, a new member of the cytoplasmic PTP family, from a cDNA library of adult colon tissue in 1992.[15] The PTPN12 gene is located on chromosome 7q11.23. It encodes a protein of about 60KD and contains 510 amino acids. The phosphatase domain of the PTPN12 protein is located at the n-terminal, while the hydrophilic c-terminal contains a potential PEST sequence, which is rich in proline (P), glutamic acid (E), serine (S), and threonine (T). The classical PTPs consist of 38 members and are divided into two families, including 21 receptor PTPs (PTPR) and 17 non-receptor PTPs (PTPN). As an important member of the non-receptor protein tyrosine phosphatase family, PTPN12 phosphorylates target specific proteins, antagonize the activity of protein tyrosine kinases, and play a crucial role in cell growth, proliferation, and movement.[16] Studies have found that PTPN12 negatively regulates the HERG channel current. The mechanism is mainly related to the decrease of the phosphorylation level of HERG tyrosine residues.[17] Subsequently, successive studies have found that the PTPN12 gene is down-regulated in many cancers such as lung cancer, breast cancer, and liver cancer.[18–20]

3.2. The critical pathway of PTPN12: Ras-Raf-MEK-ERK

Although PTPN12 has multiple downstream signaling pathways, the Ras-Raf-MEK-ERK pathway is 1 of the most important and well-known, as it plays a significant role in cell growth, cell differentiation, the mitotic cycle, and carcinogenic transformation. Moreover, there is a tight correlation between PTPN12 and the Ras-Raf-MEK-ERK signaling pathway. Studies have shown that PTPN12 negatively regulates the Ras-Raf-MEK-ERK signaling pathway through the SHC protein activated by dephosphorylation.[16] When a gene mutation occurs in PTPN12 that makes the activity of PTPN12 decrease, the mutant PTPN12 cannot dephosphorylate and activate SHC, which weakens the inhibitory regulation of the Ras-Raf-MEK-ERK pathway, leading to the occurrence of tumors.

The Ras/Raf/MEK/ERK pathway is also known as the ERK pathway. This pathway is mainly composed of a tertiary enzyme-linked functional unit. Raf, MEK, and ERK kinase are phosphorylated and activated successively. The reaction is performed through the guanylate exchange factor SOS, forming a SHC-Grb2-SOS complex with a binding protein returned to the tyrosine phosphorylation receptor.[21] Ras is activated by binding to guanosine triphosphate in response to extracellular signal stimulation, then activates Raf by phosphorylation. Next, MEK is activated by Raf and MEK finally activates ERK through phosphorylation. The phosphorylated ERK enters the nucleus and initiates transcription of multiple transcription factors. Through this signaling pathway, extracellular stimulation signals are transmitted to the cell, causing a series of cell reactions, activating a large number of transcription factors in the nucleus, and changing the expression of the corresponding genes, thereby regulating cell proliferation, differentiation, apoptosis, and metastasis, and promoting excessive proliferation of tumor cells.[22]

The Ras-Raf-MEK-ERK protein signaling pathway is a classical signaling pathway that regulates the growth and proliferation of normal tissues and cells, which plays an important role in maintaining its stability. This pathway is composed of many signaling proteins. The abnormal expression of any of these proteins would activate the pathway, causing abnormal proliferation of cells and leading to malignant transformation of cells and further formation of tumors. Abnormal activation of this pathway has been found in tumors such as colorectal cancer (CRC), liver cancer, and non-small cell lung cancer.[23–25]

In conclusion, as a tumor suppressor gene, PTPN12 is closely related to the occurrence of various tumors. Tumors are inhibited via the negative regulation of the Ras-Raf-MEK-ERK signaling pathway. On the contrary, the inactivation of the tumor suppressor gene will lead to a weakened negative regulation of the Ras-Raf-MEK-ERK signaling pathway, which causes the occurrence of tumors.[26] Therefore, in the future, we can activate the activity of the PTPN12 gene via certain methods, to control the occurrence of tumors.

3.3. Regulatory mode of PTPN12 in cancer

PTPN12 is a tumor suppressor gene that inhibits malignant cell proliferation, tumor formation, and metastasis.[27,28] The protein

encoded by PTPN12 is a member of the PTP family, which is involved in cell growth, differentiation, and the cell cycle.[29] Abnormal expression of PTPN12 has been reported in the literature to be associated with a variety of malignancies, such as breast cancer, ovarian cancer, hepatocellular carcinoma (HCC), and prostate cancer.[20,30] These cancers resulted from various regulation modes of PTPN12.

It has also been found that PTPN12 can inhibit the malignant transformation of various tyrosine kinases, such as epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor-beta.[31] The H230Y mutation of the PTPN12 protein could enhance the phosphorylation of platelet-derived growth factor receptor, leading to tumor development. In addition, the expression of PTPN12 had an important effect on the promoter methylation of cancer cell lines.[28] Moreover, PTPN12 dephosphorylated paxillin, and ultimately played a key role as an anticancer gene by inhibiting cell proliferation, migration, invasion, and epithelial-mesenchymal transformation.[31] Cyclin Dependent Kinase 2 phosphorylates PTPN12 at serine 19, thereby weakening the anticancer effect of PTPN12.[32,33]

Reactive oxygen species induced oxidation, which inactivated PTPN12 and reduced dephosphorylation, thereby promoting tumor growth.[34] PTPN12 also regulates the growth and invasion of tumor cells by mediating the phosphorylation of Cas, to regulate the ATP-dependent ubiquitin separating enzyme.[35] miR-194 negatively regulated PTPN12 to promote the development of cancerous tissues and tumor metastasis.[36]

3.4. Advances in the study of PTPN12 in related tumors

3.4.1. PTPN12 and breast cancer. Sun et al studied triple negative breast cancer and found that the PTPN12 protein appears inactive.[20] When the activity of PTPN12 protein is restored, the tumorigenicity and metastasis of breast cancer cells can be effectively inhibited. This successfully locked the PTPN12 protein as a tumor suppressor of triple negative breast cancer and identified PTPN12 as a candidate tumor suppressor gene for breast cancer. Yuan et al found that the methylation of PTPN12 resulted in gene function silencing through experiments. This showed that PTPN12 plays an important role in the occurrence of breast cancer and may be an independent prognostic factor for patients with invasive breast cancer.[37]

Subsequently, Li et al found experimentally that the expression rate of PTPN12 protein deletion in triple negative breast cancer was significantly higher than that in normal breast tissue. This result also further proved that in its inactive state, PTPN12 leads to the occurrence of tumors. Through animal experiments, Li et al found that the deletion of PTPN12 gene activity promoted the development of breast cancer cells in mouse models, which supports the view that PTPN12 serves as a human tumor suppressor.[31] At the same time, this experiment also showed that the inhibition of tumor cell survival made by the PTPN12 gene is related to the inhibition of Cas, Pyk2 tyrosine phosphorylation. Wang et al combined the clinical data and found a significant correlation between PTPN12 expression and cTNM classification.[38] They found that breast cancer patients with higher PTPN12 expression in their cells had a better clinical response to the CEX regimen, which may guide drug regimens in clinical work. Since PTPN12 was first identified as a tumor suppressor gene in breast cancer, a large number of studies have been conducted on the relationship between PTPN12 and breast cancer. The effect and mechanism of PTPN12 in controlling the development of breast cancer have been gradually revealed.

3.4.2. Digestive system

3.4.2.1. CRC. Richarda et al found that the PTP PTP-PEST encoded by PTPN12 is a regulator of cell movement, which is helpful to reduce the incidence of heterogeneity in CRC. Therefore, PTPN12 is used as a candidate for a new tumor suppressor gene for CRC.[39] Shen et al found that PTPN12 can increase the risk of CRC by modifying Ras-MEK-ERK signal transduction, which will provide new insights into the role of CRC pathogenesis.[16]

3.4.2.2. HCC. R-Z Luo et al found that decreased PTPN12 expression was closely related to the recurrence of liver cancer ($P = 0.015$).[19] Univariate analysis showed a significant correlation between decreased PTPN12 expression and relapse-free survival ($P < 0.001$). Zhang et al used Kaplan-Meier univariate and multivariate Cox proportional hazard models to assess the risk factors of survival.[40] Using a quantitative real-time polymerase chain reaction and immunohistochemistry (IHC) to detect the expression level of PTP genes, they found that PTPN12 is an independent prognostic factor for HCC.

3.4.2.3. Esophageal cancer. Using a Western blot, Cao et al evaluated the expression of PTPN12 in 20 surgically resected esophageal tissues.[41] The results showed that the expression level of PTPN12 in normal esophageal tissues was higher than that in esophageal squamous cell carcinoma tissues. After multivariate analysis, it was found that the protein expression level of PTPN12 is an independent and significant predictor ($P < .001$). Thus, it was concluded that the protein expression of PTPN12 is an important biomarker for patients with esophageal cancer. High expression of PTPN12 is associated with disease-free survival and overall survival in patients with esophageal cancer.

3.4.3. Urinary system. Piao et al measured the expression of PTPN12 gene in bladder transitional cell carcinoma by IHC and a Western blot, then determined the mRNA expression of PTPN12 gene through a reverse transcription-quantitative polymerase chain reaction.[42] They found that the expression level of PTPN12 was inversely related to tumor size, pathological grade, clinical stage, and tumor recurrence. When the expression level of PTPN12 was decreased, the bladder transitional cell carcinoma showed stronger adhesion, migration, and invasion.

3.4.4. Respiratory system. Cao et al used IHC and a Western blot to analyze the expression of PTPN12 in non-small cell lung cancer cells (NSCLC).[18] Both IHC and the Western blot showed that the expression level of PTPN12 in normal lung cancer tissues was higher than that in NSCLC tissues. At the same time, it was concluded that high PTPN12 expression level is beneficial to the 5-year survival rate of lung cancer, especially in non-NSCLC patients. Therefore, the expression of PTPN12 can be used as a marker to evaluate the prognosis of NSCLC. In addition, another study has found that the low expression of PTPN12 is closely related to radiosensitivity in NSCLC patients and the down-regulation of PTPN12 gene can significantly increase the radiosensitivity of H1299 cells.

3.4.5. Nasopharyngeal carcinoma. Through semi-quantitative immunohistochemical staining, Zhang et al found that decreased expression of PTPN12 was more frequently observed in

nasopharyngeal carcinoma tissues compared with normal nasopharyngeal mucosa.[43] Further correlation analysis showed that the decreased expression of PTPN12 was significantly associated with tumor size, lymph node metastasis, distant metastasis, and clinical stage of nasopharyngeal carcinoma ($P < .05$). Univariate analysis showed a significant correlation between decreased expression of PTPN12 and overall survival ($P < .05$). More importantly, the multivariate analysis identified the expression of PTPN12 as an independent prognostic factor in nasopharyngeal carcinoma. The decreased expression of PTPN12 may play an important role in making nasopharyngeal carcinoma more invasive. Therefore, the expression of PTPN12 can be used as a novel independent prognostic biomarker for patients with nasopharyngeal carcinoma. Lin et al cultured the nasopharyngeal carcinoma cell line CNE2 in vitro, then made a PTPN12 plasmid transfection. This can increase PTPN12 mRNA and protein expression, inhibit cell proliferation and migration, and reduce the EGFR level. So, PTPN12 can be used as a molecular target for diagnosis and prognosis analysis of nasopharyngeal carcinoma.[44]

3.4.6. Oral squamous cell carcinoma. Su et al found that the expression of PTPN12 in oral squamous cell carcinoma tissues is reduced through an experiment.[45] The decreased expression of PTPN12 was significantly associated with the clinical stage of the disease ($P < .01$). In addition, reduction of PTPN12 is associated with over-activation of signal transducers and activator of transcription 3 (STAT3). PTP receptor type D is negatively correlated with the phosphorylation of STAT3 ($R = -0.535$). The low expression of PTPN12 and the high phosphorylation of STAT3 are related to a poor prognosis. Overexpression of PTPN12 inhibits the proliferation and migration of oral squamous cell carcinoma cells. PTPN12 is associated with STAT3 and induces STAT3 dephosphorylation. Therefore, we can conclude that PTPN12 may play a role through STAT3 binding and dephosphorylation. So, PTPN12 is a potential marker for prognostication of oral squamous cell carcinoma.

3.4.7. Gynecological oncology. Villa-Moruzzi et al found that PTPN12 directly acts on focal adhesion kinase in a her2-dependent manner, causing a negative regulation of the migration of ovarian cancer cells.[30] Liang et al found that mir-194 is overexpressed in ovarian cancer cells through real-time polymerase chain reaction (RT-PCR).[36] Overexpression of mir-194 promotes cell proliferation, migration, and invasion. A luciferase assay showed that mir-194 directly bound to the non-coding region of PTPN12. In the meanwhile, through a Western blot and quantitative real-time polymerase chain reaction, researchers showed a negative correlation between PTPN12 expression and mir-194 expression in ovarian cancer tissues. Therefore, it was concluded that miR-194 directly acts on the PTPN12 gene and inhibits its activity, which leads to the occurrence of ovarian cancer. This also indirectly confirms the assertion that the PTPN12 gene is a tumor suppressor gene.

3.4.8. Glioblastoma. Glioblastoma is an invasive brain cancer in which tumor cells are often scattered from the primary mass to escape surgical removal, leading to a fatal recurrence. A cytoplasmic PTP (PTP-PEST) was reported to control the invasion of glioblastoma cells by physically bridging the plaque, binding the Crk-related substrate to the valin-containing protein (VCP).[35] Based on previous screening and recent research results, it was found that the levels of VCP and PTP-PEST mRNA in different glioblastoma regions were negatively correlated, suggesting that the expression of PTPN12 and VCP in glioblastoma regions may be related to gene regulatory events.[46] The data showed that PTPN12 had a specific role in the differential regulation of growth survival and migration. In glioblastoma cells with low expression of PTPN12, the association between the receptor tyrosine kinase and beta 8 integrin might be changed, resulting in reduced growth but increased invasiveness. Thirty-five copy number variants of the germ line were predicted in 107 available paired blood samples from glioblastoma patients. Many predictions of copy number variants of somatic cells in glioblastoma involved PTPN12, suggesting that PTPN12 was very common in glioblastoma through various rearrangements and regulation.[47] PTPN12 was known to dephosphorylate the oncogenes c-abl and Src, and PTPN12 may contribute to tumor survival.[48] Given the number of rearrangement candidates for PTPN12, the most important factor for glioblastoma might be the regulation of PTPN12, not necessarily any single rearrangement.

3.4.9. Melanoma. The main driver of melanoma progression is cytogenetic heterogeneity due to chromosomal instability. One study examined chromosomal changes in a group of melanoma cell lines based on the aCGH atlas, showing that chromosome loss in the 7q region seems to be associated with aggressive behavior. MRNA expression analysis provided the first evidence that structural and functional changes in PTPN12 genes play an important role in melanoma invasion.[49] When the 12q chromosomal regions was increased or the 7q was absent in the PTPN12 genes, the mutation frequency of melanoma cells would be enhanced, and the invasiveness was exasperated. Koroknai identified that the mRNA level of PTPN12 was related significantly to copy number changes.[50] There are few studies on the correlation between melanoma cell invasiveness and the PTPN12 gene. Further functional research is necessary.

4. Discussion

In 2011, Sun found that PTPN12 protein was inactivated in a study of triple negative breast cancer. When PTPN12 restored its activity, it could effectively inhibit tumorigenicity and metastasis of breast cancer cells. Therefore, the PTPN12 protein was successfully identified as a tumor suppressor of triple negative breast cancer, and the PTPN12 gene was identified as a candidate tumor suppressor of breast cancer.[20] Since then, the prognosis and treatment of PTPN12 and related tumors have been studied extensively. Luo[19] found that the decreased expression of PTPN12 was not only closely related to the occurrence of liver cancer, but also significantly correlated with the recurrence rate and survival rate of liver cancer. By using real-time quantitative PCR and a Western blot to detect the expression of PTPN12 at the mRNA and protein levels, Cao found that high expression of PTPN12 was related to the overall survival of patients with non-small cell lung cancer, and suggested that PTPN12 was a better biomarker.[18] This is a good attempt to transition PTPN12 gene from the experimental level to clinical treatment. However, little is known about the study of PTPN12 and kidney cancer, and the effect of PTPN12 on the occurrence and prognosis of kidney cancer needs to be further confirmed.

Existing studies have confirmed that PTPN12 has a regulatory effect on tumor cell migration.[51] PTPN12 is often absent in cell lines and tumor tissues of triple-negative breast cancer. It can block the signaling pathways of carcinogenic receptors such as

EGFR and HER2, and thus inhibit the malignant proliferation of breast cells.[28] Similar effects are also reflected in the occurrence and development of other tumors, such as renal cell carcinoma[34] and nasopharyngeal carcinoma.[44] Moreover, the combination of Czotinib and Sonitinib showed a strong drug interaction in the PTPN12-sensitive triple-negative breast cancer model, but it did not inhibit the growth of PTPN12-resistant triple-negative breast cancer cells. The research results showed that PTPN12 could be used as a negative feedback regulator for carcinogenic receptor tyrosine kinases.[28]

In addition, CD148 has been identified as part of the R3 subtype in other PTPs such as vascular endothelial PTP, glomerular epithelial protein-1, gastric cancer related PTP-1, and receptor tyrosine phosphatase Q.[52] Takahashi developed a monoclonal antibody against the CD148 extracellular domain and studied the effect of this antibody on endothelial cell growth. In the measurement of corneal angiogenesis in vivo in mice, this antibody inhibited the growth of endothelial cell lines and blocked angiogenesis.[53] Two CD148 ligands, platelet reactive protein 1 and syndecan-2, have also been reported in existing studies.[54,55] Both ligands have similar effects on tumor cell growth. Tsp-1 can increase the catalytic activity of CD148, lead to the dephosphorylation of substrate proteins, and inhibit the growth of endothelial cells. The interaction of CD148 with syndecan-2 stimulates cell adhesion and adhesion plaque formation, which may lead to the downregulation of cell proliferation and growth.[56]

Therefore, the PTP family mainly regulates the development and progression of malignant tumors, such as angiogenesis and malignant cell proliferation, by regulating the signaling pathways of various growth factor receptors. The difference is that the high expression of PTPN12 in the treatment of malignant tumors can regulate the occurrence and development of tumors and enhance the sensitivity of malignant tumors to targeted drugs. In contrast, inhibition of other members of the PTP family, such as vascular endothelial PTP, glomerular epithelial protein-1, and gastric cancer-related PTP-1, can also play a role in tumor development and progression during the treatment of malignant tumors.

5. Conclusion

To sum up, the essence of tumors is genetic diseases. To put it simply, the balance between oncogenes and tumor suppressor genes is broken. Inhibiting the activity of PTPN12, a tumor suppressor gene, will lead directly or indirectly to the occurrence of tumors. Renal cell carcinoma, the most common malignant tumor of the urinary system, is urgent to diagnose early and treat early. Renal cancer genetic testing and tumor marker testing are still immature. In the development of research, PTPN12 may serve as a new molecular marker to benefit patients, and even the development of tumor suppressor gene activation agents can form a practical research direction.

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Author contributions

Bin Liu and Yu-hu Huo performed the investigation and were major contributors towards manuscript writing and submission. Ling-bing Meng made substantial contributions towards conceptualizing the research. He also designed a draft of the research process. Ya-ni Wang were involved in developing the intervention and study protocol. Ai-li Zhang critically revised the manuscript for important intellectual content. He modified the manuscript format, discussed reviewer opinions, and clarified the professional terms. All authors read and approved the final manuscript.

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