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Research Progress of Protein Tyrosine Phosphatase Receptor-Type O in Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in the world with a high incidence and has become one of the most malignant cancers worldwide. Its clinical treatment mainly includes surgical intervention, chemotherapy, and immunotherapy, with poor curative effect and prognosis. In recent years, with the development of basic research, it has been revealed that protein tyrosine phosphatase receptor-type O (PTPRO) plays an important role in the pathogenesis of hepatocellular carcinoma. Protein tyrosine phosphatase receptor-type O is a new type of protein tyrosine phosphatase, which has been proven to inhibit oncoprotein. In this paper, the potential mechanism of protein tyrosine phosphatase receptor -type O in the progression of hepatocellular carcinoma is discussed to provide reference for clinical treatment and drug development.

Keywords: Protein tyrosine phosphatase receptor-type O; Hepatocellular carcinoma; Research progress

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1. Background

In the past 20 years, the incidence rate of hepatocellular carcinoma (HCC) globally has been increasing. About one of every two HCC patients come from China [1]. It is the fourth most common malignancy in China and the second most common cause of cancer-related deaths after lung cancer. It seriously threatens human life and affects the health as well as the quality of life of human beings. Protein tyrosine phosphatase receptor-type O (PTPRO) gene is closely related to tumors. As a candidate tumor suppressor gene, its mechanism is not completely clear. The gene can show different regulatory effects in different immune microenvironments. On the one hand, it can dephosphorylate downstream proteins and inhibit tumors by inhibiting downstream pathways; on the other hand, if the exon of the protein is methylated, the expression of the protein decreases, leading to the growth of tumors. It affects cell biological behaviors, such as tumor cell proliferation, apoptosis, and transformation; its mediated autophagy also plays an important role in the transformation of nonalcoholic steatohepatitis (NASH) to HCC. This paper mainly discusses the role of PTPRO in the transformation from inflammation to HCC.

2. Transformation from inflammation to HCC

A large number of studies have confirmed that inflammation can promote the occurrence, development, infiltration, and metastasis of tumors [2]. Inflammatory response itself is also a process of host defense. It participates in the clearance of foreign pathogens, the repair of tissue damage, and in some cases, it also promotes the decline of tumors. The most important risk factors for HCC are chronic hepatitis B, hepatitis

C, aflatoxin B1 exposure, and NASH, in which its incidence has been increasing in recent years due to the increasing incidence rate of obesity and type 2 diabetes [3]. The chronic development of hepatitis B, hepatitis C, NASH, and other diseases may lead to fibrosis as well as cirrhosis. In the progressive development of the disease, self-repair occurs by means of activating the regeneration potential of liver cells and breaking immune tolerance, which ultimately leads to the occurrence of HCC. Nowadays, with the improvement of human living standards, obesity is common among people. NASH, caused by obesity, has undoubtedly become the main reason that promotes the significant increase of liver cirrhosis and liver cancer. Therefore, it is necessary to pay special attention to the role of NASH in HCC. During the gradual transition from inflammation to HCC, it is possible to prolong the life cycle of patients and reduce the incidence of liver cirrhosis as well as liver cancer by controlling chronic inflammation, reducing the prevalence of obesity, reducing alcohol consumption, and reinforcing exercise. It has been found that PTPRO plays an important role in inflammation as well as the occurrence and development of liver cancer. It participates in the growth and differentiation of cells as well as the transformation of oncogenes; it affects cellular immunity through methylation, phosphorylation, and PTPRO-mediated autophagy as well as participates in the regulation of inflammatory response, thus affecting the occurrence, development, proliferation, and apoptosis of tumor cells [4]. PTPRO gene is located on human chromosome 12. If it is deleted or inactivated, it would lead to the loss of regulation of cell cycle and the massive expansion of some proto-oncogenes, thus eventually leading to tumorigenesis.

3. Methylation and phosphorylation of PTPRO

The most common methylation modifications in tumors are DNA methylation, histone methylation, RNA methylation, epigenetic changes, and stimulation by internal and external factors; they may lead to diseases and even tumors [5]. One of the reasons why epigenetic silencing of tumor suppressor genes occurs is the hypermethylation of the promoter region. PTPRO promoter methylation has been found in rat models of hepatocellular carcinoma and human lung cancer. PTPRO overexpression can inhibit the proliferation of cancer cells and promote cancer cell apoptosis, suggesting that PTPRO gene can inhibit tumors. In addition, studies have suggested that PTPRO methylation also exists in anaplastic large cell lymphoma and multiple myeloma [6]. In the future, DNA methylation is expected to become a new tumor marker and play an important role in tumor therapy. SET7/9 is a member of the protein lysine methyltransferase family. The occurrence of methylation can affect the process of cell growth, proliferation, and apoptosis. It plays a carcinogenic role in HCC. SET7/9 imbalance is often detected in human oncogenes [7]. Protein tyrosine kinase (PTK) and protein tyrosine phosphatase (PTP) can regulate the reaction of phosphorylation and dephosphorylation and control the opening and closing of a large number of cellular signal pathways. Protein dephosphorylation, an important function of PTPRO, participates in the signaling pathway to regulate the level of substrate protein, which is closely related to the tyrosine phosphorylation of the carboxyl terminal motif of the gene. If the relative dynamic balance between PTK and PTP is maintained, a series of physiological processes such as cell proliferation, differentiation, and metabolic apoptosis would be relatively stable. The expression of PTPRO decreases with the development of HCC, having a relation to the tumor size and TNM stage. It has been found that after PTPRO gene deletion, the activities of Janus kinase 2 (JAK2) and phosphatidylinositol 3-kinase (PI3K) increase significantly, downregulating the signal transduction as well as inhibiting the signal transducer and activator of transcription 3 (STAT3). The activity promotes the significant upregulation of the phosphorylation levels of Y705 and S727 sites of STAT3 and finally realizes the inhibitory effect on tumor. This inhibition is related to the loss of STAT3 activity. Therefore, PTPRO plays a tumor inhibitory role through the phosphorylation of STAT3 [8,9].

4. Mechanism of PTPRO mediated autophagy in NASH-HCC

Under normal circumstances, autophagy can inhibit tumorigenesis by renewing some necrotic organelles and participating in apoptosis. Once oncogenes are formed, autophagy would promote tumor development [10]. The study found that during the transformation from inflammation to HCC, obesity, elevated triglycerides, hyperinsulinemia, reactive oxygen species deposition, and other factors may damage liver function, trigger a series of inflammatory reactions, and finally promote the growth of HCC. Similarly, in HBV and HCV carriers, the risk of HCC in obese people is more than 100 times higher than that in people with normal weight. Promoting autophagy can degrade lipid droplets and reduce fat accumulation in the liver as well as liver damage [11]. In the development of NASH-HCC, PTPRO deficiency can aggravate hepatic steatosis and induce tumorigenesis. In a mouse model of NASH-HCC, Western blot was used to detect the expression of autophagy markers, LC3 and P62, in wild C57BL/6 mice, and WB was used to analyze the expression of autophagy markers, LC3 and P62, in PTPRO knockout mice liver tissues. Over time, it was found that the expression of PTPRO in wild mice fed with high fat gradually decreased and the autophagy activity from being continuously inhibited before tumor formation increased after tumor formation. In PTPRO deficient mice, the LC3-II/I ratio, which is an important marker of autophagy inhibition, decreased, and the expression of P26 protein increased, indicating that PTPRO can regulate lipid metabolism and the autophagy activity of cells [12].

Disclosure statement

The authors declare that there is no conflict of interest.

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