The Progress of TSP-1 in the Research of Various Kinds of Related Tumors

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Abstract

Thrombospondin 1 (TSP-1) as a kind of inhibiting angiogenesis important substances, widely distributed in human tissues, but also makes it occupy the irreplaceable position in the formation of different tissues of tumor, growth, differentiation, metastasis, currently available in the literature about TSP-1 in various types of cancer (such as prostate cancer, bladder cancer, non-small cell lung cancer, breast cancer, cervical cancer, pancreatic cancer, etc.) the occurrence and development of the role of the reported It is often seen. It undoubtedly provides new directions and guidelines for medical science research workers in the field of cancer and its relationship with tumor would has irreplaceable role for prognosis and exploration the clinical tumor's etiology, diagnosis and treatment. This review is a summary of the discovery and development of TSP-1 in various types of tumor research.

Keywords: Thrombospondin 1 (TSP-1); CD47; Solid tumors; Blood system malignant tumor

Introduction

TSP-1 is a multifunctional glycoprotein, be synthesized and secreted by platelets, epithelial cells, mesothelial cells, mesangial cells, fibroblasts etc. It could active the transforming growth factor beta, inhibiting angiogenesis and anti tumor activity, participates in tissue repair biological effects [1,2]. TSP-1 can regulate tumor cell growth, adhesion, migration and other biological behavior [3]. The thrombin sensitive protein, as the most powerful tumor angiogenesis negative regulator, regulates angiogenesis of solid tumor, which has important effects on the generation, development, treatment and prognosis of solid tumors [4,5]. Cancer treatment or through the regulation of the immune system to achieve the purpose to improve the anti-tumor effect, the human immune system or by the secretion of silver or direct regulation of tumor angiogenesis so as to achieve the purpose of tumor cure and control [6]. The application of immune histochemical study found that some of the human tumor cell lines (such as squamous cell carcinoma, melanoma, breast cancer, etc. also have a synthesis of TSP-1). Recently in the treatment of cancer immunotherapy drugs have provided significant progress, in some cases, with superior efficacy. MN McCracken and other experiments [7] have found that CD47 as an important "do not eat me" signal expressed in the malignant cells. CD47 blockade [8]: SIRP-α axis tumor cells and immune cells (monocytes, macrophages, and dendritic cells) increased tumor cell phagocytosis in solid tumors (including, but not limited to, bladder, breast, colon, lung and pancreas) [9] and blood system malignant tumor. These innate phagocytic cells are also specialized antigen presenting cells (APC), which provides a link to the innate adaptive tumor immunity. Preliminary study showed that the APC antigen was engulfed by tumor cells, which activated T cells. Thus, drug blocking CD47: SIRP - alpha employs attractive therapeutic targets as monotherapy or in combination with other immune modulators to activate T cells *in vivo*. *In vitro* and in tumor bearing mice model were found in closed CD47 or after the up-regulated expression of TSP-1, SIRP - alpha through signaling pathway increasing the degree of infiltration of macrophages around tumor cells and its effect on tumor cells so that the tumor area decreased. TSP-1 at physiological concentrations can be through the C and endothelial cells on the CD47 molecule binding, inhibit the NO signal transduction pathway to regulate blood vessel formation process, blood flow, as well as the role of blood platelets [10-12]. Tumor associated angiogenesis is assumed to be regulated by a balance between pro angiogenic factors and anti angiogenic factors. RS Watnick is a key step in the establishment of the angiogenesis ability of human tumor cells, which is a key factor to inhibit the secretion of anti angiogenic factors, platelet reactive protein -1 (TSP-1). This

inhibition is expressed by the mammary epithelial cell and renal cell engineering SV40 early interval gene protein, hTERT and H-RasV12, which are essential for tumor formation. In the process of epithelial cell transformation, a signaling pathway leads to a reduction in PI3 kinase induced order activation from Ras to TSP-1, Rho and ROCK, which activates Myc by phosphorylation, thus enabling myc to inhibit TSP-1 transcription. However, in the change of fibroblasts, TSP-1 inhibition can be achieved through another mechanism involving p53 and pRb inactivation. We describe a novel mechanism by which the activation of epithelial cancer genes and the inactivation of tumor suppressor genes, in turn, enable tumor formation through the activation of fibroblasts in the fibroblasts [13].

Materials and Methods

In bladder cancer it was found that the expression of TSP-1 was closely related to the stage and stage of bladder cancer [14], in the higher stage and high degree of malignancy were weak expression of TSP-1 expression, the higher positive rate of specimens in normal tissue or tumor early. Wang Xiaohui, Li Zhijun to detect human bladder transitional cell carcinoma (TBCC) for the relationship between the expression of CD105 and TSP-1 and the clinical pathological features of TBCC, the expression level for 60 cases of bladder carcinoma and 12 cases of normal bladder mucosa tissue was used to determine the CD105 and TSP-1 by S-P and micro vessel density (MVD), and the analysis of transitional cell carcinoma staging and grading of the expression and its significance in bladder. The positive expression rate of CD105 in 60 cases of transitional cell carcinoma of bladder was 78.3%, and the positive expression rate of TSP-1 was 43.3%.The expression of CD105 and micro vessel density (MVD) in bladder transitional carcinoma was significantly higher than that in normal bladder tissues ($P < 0.01$). There was no significant difference in the expression of TSP-1 in the early transitional cell carcinoma of bladder ($P > 0.05$), and the expression was lower than that in the normal bladder tissue ($P < 0.05$). It was found that the expression of CD105 and TSP-1 in TBCC was an important factor to regulate tumor angiogenesis, which was closely related to the growth and metastasis of tumor. Yap and other research confirmed that TSP-1 derivatives can directly kill endothelial cells *in vitro*, *in vivo* can induce the apoptosis of endothelial cells induced by cyclophosphamide and cisplatin, thereby inhibiting the formation of tumor angiogenesis [15]. A number of studies have found that the combination of TSP-1 and vascular endothelial receptor CD36 inhibits the migration of endothelial cells and the formation of capillary vessels. Isenberg and other studies have found that the type sequence of TSP-1 can significantly inhibit the proliferation of endothelial cells [16]. Reiher et al. [17] also found that TSP analogues of DI-TSP have similar inhibition of tumor angiogenesis and TSP-1 induced endothelial cell apoptosis. The expression of -1 (TSP-1) plays an important role in bladder cancer. To investigate the distribution of TSP-1 696 C / T polymorphism (rs2664139) relationship between clinical features of bladder cancer and the genotype was determined in 609 cases and 670 cases of control group by fluorescence method in Chinese crowd. Jinbao Gu and other multiple regression analysis were used to analyze the relationship between polymorphisms and bladder cancer risk, and the results showed that the TSP-1 - 696 C / T polymorphism may have an influence on the susceptibility of bladder cancer in Chinese population [18].

In the absence of TSP-1 breast cancer in animal tumor burden and vascular system significantly increased [19], within the tumor capillary expansion; high expression of TSP-1 mice showed delayed tumor growth or lack of tumor progression. The expression level of TSP-1 in breast cancer was negatively correlated with the density of blood vessels in the breast cancer tissue. In the same cancer tissue [20], the TSP-1 expression level was higher than that of the local vascular density. The recurrence and metastasis of breast cancer depend on the angiogenesis of tumor tissue. Wang Wensheng [21] to explore the role of TSP-1 and VEGF in breast carcinoma invasion, metastasis, recurrence and prognosis, by using immunohistochemical S-P method in 180 patients with breast cancer, according to the Neufeld scoring method, using χ2 test and Person correlation analysis, using SPSS17.0 statistical analysis software package. TSP-1 (+) cases of the recurrence rate is TSP-1 (-) were low, said TSP-1 may to some extent limit the recurrence and metastasis of breast cancer. Prolactinoma is the most common type of human pituitary tumors, the dopamine receptor agonist in the treatment of common reaction is good, but for the dopamine antagonist drugs patients need to adopt alternative therapies, TSP-1 high expression of prolactinoma. Its growth is relatively slow, less metastasis, and angiogenesis is reduced, so TSP-1 may provide a new target for cancer the treatment. Recouvreux MV and other studies suggest that TSP-1 may act as a potential replacement therapy or supplement for dopamine receptor agonists [22].

At present, the clinical diagnosis of prostate cancer mainly rely on rectal examination, serum PSA, rectal ultrasound and pelvic MRI examination, diagnosis is required by the prostate biopsy. Based on a large number of studies, the problem of excessive diagnosis and treatment of PSA in the pre - screening of adenocarcinoma was found. In 2007 Shafer to solve this problem, taking into account the forefront of prostate cancer patients with TSP-1 had higher frequency in 22 kinds of disease related protein in 80% [23-25], the TSP-1 as a new diagnosis of prostate cancer and benign prostatic hyperplasia index, through certain methods and experiments the sensitivity and specificity of TSP-1 were better than that of up to 79% and 81%, Bastian [26], in prostate cancer TSP-1 synthesis in partial or total loss can provide some favorable conditions for the growth of tumors. After Wang Jianye, Zhang Yao guang and so on through the self - designed enzyme linked immune sorbent assay (ELISA) to diagnose the sensitivity and specificity of routine PSA comparison, the results of TSP-1 ROC area is 0.9663 (SE=0.0299), PSA ROC (SE=0.0909) area of 0.7421, the difference was statistically significant ($P < 0.05$) the value of TSP-1, smaller differences between individuals, PSA fluctuations, prostate cancer TSP-1 value [(73.77 + 12.72) and detected in benign prostatic hyperplasia (121.86 + 19.47)%] patients were compared, the difference was statistically significant (t=8.44, $P < 0.01$), so TSP-1 PSA can more accurately distinguish benign and malignant prostate disease. Immuno histochemical expression of TSP-1 two step method of benign prostatic hyperplasia group was significantly higher than that in prostate cancer group ($P < 0.05$). The expression of TSP-1 was significantly higher in the low score group and non bone metastasis group than in the high score group and the bone metastasis group ($P < 0.05$). TSP-1 is an important index to judge the malignant degree and prognosis of prostate cancer [27,28]. TSP-1 and PEDF two molecules in prostate cancer cells were reduced, and its development is associated with increased angiogenesis, thrombospondin (TSP - 1) and pigment epithelium derived factor (PEDF), anti angiogenic molecules can effectively reduce the expression of prostate cancer cells. TSP-1 exerts its activity by binding to cell surface receptors such as CD36, which can inhibit the growth of prostate cancer by

inhibiting the formation of tumor blood vessels [29].

CD47 blockade may inhibit thrombin sensitive protein -1 signal or prevent the inhibition of SIRP tumor associated macrophage growth signal [30] control liver tumor research [on the apoptosis of human hepatoma cell line HCCLM3 *in vitro* induced effects and mechanisms of [31], cell apoptosis by flow cytometry TSP-1 and its receptor CD36, CD47 induced HCCLM3 rate the application of electron microscopy analysis, morphological changes after the reverse transcriptase polymerase chain reaction (RT-PCR) expression in HCCLM3 cells after caspase-3mRNA analysis, found that the apoptosis rate of TSP-1 Group [(12.44 + 0.72)%] was significantly higher than the control group [(4.31 + 0.29)%] and CD47 blocking group [(4.99 + 0.12)%], P < 0.01. CD36 blocking group [(9.99 + 0.57)%] higher than the control group or CD47 blocking group, lower than the TSP-1 group (P < 0.01). Electron microscope observation of the control group and CD47 blocking group cells growth, TSP-1 group and CD36 blocking group apoptosis rate increased, the cells showed a variety of apoptosis. The expression of caspase-3mRNA in group TSP-1 (0.652 + 0.024) and CD36 blocking group (0.615 + 0.020) was significantly higher than that in control group (0.398 + 0.033) and CD47 blocking group (0.432 + 0.019), P < 0.01. TSP-1 can induce the apoptosis of human hepatoma cell line TSP-1, HCCLM3 and receptor CD47 binding up regulation of Caspase-3 expression may be one of the pathways, and the invasion and metastasis of hepatocellular carcinoma [32].

Low expression of TSP-1 in non small cell lung cancer is an indicator of poor prognosis [33,34] plays a very important role in the invasion and metastasis. Wang Chunling [35] through the examination of 45 cases of non-small cell lung cancer (NSCLC) ET-1 and 18 cases of normal lung tissues, the expression of TSP-1 and microvessel density (MVD) count, found ET-1 positive expression rate of NSCLC in (42.22%) was significantly higher than the control group, the expression of NSCLC and ET-1 histological there is a close relationship between the grade and lymph node metastasis, ET-1 MVD positive group was significantly higher than ET-1 negative group. The positive expression rate of TSP-1 in NSCLC (37.78%) was lower than that of control group, and the expression of TSP-1 was related to lymph node metastasis. The MVD of TSP-1 positive group was lower than that of TSP-1 negative group. The expression of MVD was positively correlated with the expression of TSP-1, and negatively correlated with the expression of ET-1. Which shows that in NSCLC ET-1 as an angiogenic factor, TSP-1 acts as an inhibitor of angiogenesis factor and angiogenesis of lung cancer, both have a synergistic effect, decreasing the expression of TSP-1 NSCLC in the invasion and metastasis play an important role in increasing. The joint detection is helpful to judge the metastasis and invasion of NSCLC. The objective basis is provided to judge the degree of differentiation and treatment outcome of NSCLCN. Puri N and other studies have found that the synergistic action of T-oligo and TSP-1 in non-small cell lung cancer can reduce tumor size and inhibit angiogenesis [36]. About Osteopontin (OPN) and thrombospondin -1 (TSP-1) effect on prognosis in patients with non-small cell lung cancer, M and Rouanne were analyzed retrospectively in 171 cases of non-small cell lung cancer patients from 2012 January to December after radical surgery, preoperative serum, demographic, clinical and pathological data were analyzed analysis and molecular. Determination of serum OPN and TSP-1 before treatment by ELISA. The expression was detected by immuno histochemistry in primary tumor tissue protein, the results showed that before treatment the serum OPN and TSP-1 levels can reflect tumor aggressiveness and prognosis of primary non-small cell lung cancer patients can be used as markers of surgical resection [37].

Results

The development may be reduced to inhibit angiogenesis and expression of TSP-1 protein in uterine leiomyoma, promote apoptosis and expression of IGF- II expression to promote tumor angiogenesis, promote cell proliferation related. The expression of TSP-1 in uterine leiomyoma was lower than that in normal uterine muscular layer [38].

According to the experimental study of H Laklai revealed TSP-1 on pancreatic cancer angiogenesis and pancreatic cancer cells are inhibited, the somatostatin receptor subtype 2 (SST2) and the expression of TSP-1 in pancreatic cancer is up-regulated anti tumor effect of early pancreatic cancer negative feedback inhibition [39]. Linhai and other researchers found that the expression of TSP-1 in pancreatic cancer was significantly higher than that of normal pancreas and chronic pancreatitis tissues (P < 0.05). Different tumor stages and different tumor size, lymph node metastasis, perineural invasion of pancreatic cancer patients without TSP-1 expression had significant difference (P < 0.05); Logistic regression analysis show that the expression of TSP-1 and tumor stage, perineural invasion is closely related to the Kaplan-Meier method and Log-rank test analysis showed that the expression of TSP-1 and lymph node metastasis, neural invasion, tumor stage and patient survival rate; multivariate COX risk model analysis showed that the neural invasion, lymph node metastasis and tumor prognosis is directly related to TSP-1 expression is not directly related. It comes out that TSP-1 can be used to judge whether the transfer of the pancreatic cancer index to judge the prognosis of pancreatic cancer has a certain clinical value. The resistance of oxaliplatin therapy of gastric cancer is the main reason for its failure, which found that the drug resistance gene in oxaliplatin by the alcohol resistance gene 1 (Txr1), the research of taxol show that in oxaliplatin resistant cell SGC7901 / L transfer mainly expressed the site of TXR1 from the nucleus to the cytoplasm, the expression of TXR1 mRNA and protein were higher than the parental cells and the expression of thrombospondin 1 (TSP1) decreased. When the TXR1 gene silencing, increase the expression of TSP1 and oxaliplatin on human gastric cancer cells significantly reduced oxaliplatin.TSP-1 may exert a positive effect on the treatment of gastric cancer by inhibiting the production of drug resistance of gastric cancer cells by the coordination of TXR1 with [40].

G Bocci et al. [41] in the evaluation of the mechanism of the anti angiogenic activity of ceramide analogues, it is found that in the process of TSP-1 and other related factors, the effects of anti tumor and anti angiogenesis are increased. Local blood perfusion and angiogenesis of malignant glioma is an important factor in its growth, must guarantee perfusion rate to allow their growth, while TSP-1 can significantly inhibit the angiogenesis and reduce local perfusion, so as to achieve the purpose of slow or even inhibit the growth of [42].

H Naganuma and other studies show that the expression of TSP-1 protein is regulated by the normal cell density of glioblastoma cells, rather than by the density of the tumor cells [43]. MVD is an independent index of malignant hematological disease. TSP-1 is a negative regulator of angiogenesis, which can help to evaluate the severity and efficacy more accurately and guide the clinical treatment. TSP-1 can also on multiple myeloma treatment and prognosis to predict and evaluate the effect of [44,45] glioma is the most common central nervous system primary tumor angiogenesis with vascular rich features, to study the molecular mechanism of potential angiogenesis,

to help identify therapeutic targets the potential has an important role in the study of Jing, Zhang and TGF- show that the TSP-1 beta gamma PPAR- expression in glioma and tumor microvessel density was negatively correlated, suggesting that inhibition of formation of these proteins may be involved in glioma angiogenesis [46].

Cutaneous melanoma expressed pleiotropic factor thrombospondin-1 (TSP-1). A study suggests that TSP-1 can change the morphology and function of blood vessels, thus the growth and metastasis of melanoma plays a certain role in [47], but the study of Borsotti P showed that the TSP-1 (RNA and protein), in four cultured melanoma cells and RGP melanoma were not detected in, from 13 a cell line at present advanced melanoma or metastasis in. In addition, 55 people in the disease gene chip analysis showed that the expression of primary melanoma and metastases TSP-1 than common dysplastic nevi, and melanoma cells TSP-1 production movement *in vitro* and *in vivo* on lung colonization potential. VEGF, VEGFR-1 and FGF-2, to participate in the development of melanoma, regulate the production of TSP-1. The co-expression of these factors was negatively correlated with TSP-1 and SNAI2 (SNAI2), the main gene of cell migration was closely related to the metastasis of melanoma. The results showed that TSP-1 and FGF-2, VEGF and VEGFR-1 together, as part of an independent movement plan to determine the invasion and metastasis of melanoma [48]. A Jeanne found that thrombospondin -1 (TSP-1) is an extracellular matrix glycoprotein is known for its high expression in the tumor microenvironment, it can promote a positive phenotype in particular by interaction with cell surface receptors of the CD47 effect. In many malignant tumors, its origin in the stroma, melanoma is an exception, invasion and metastatic melanoma cells over expression TSP-1. The recent study shows that a molecule of new drugs selectively prevents CD47 from binding to TSP-1, called TAX2, when administered systemically, by reducing the B16 melanoma subcutaneously transplanted tumor tissue to exhibit anti-cancer properties. At the same time, new evidence is presented to support the contribution of TSP-1 in the treatment of melanoma metastasis and resistance. Based on the analysis of multiple genomic and proteomic databases based on a comprehensive system biology approach, the first identified a tsp-1-centered interactive network for high expression in metastatic melanoma. Then, the effects of disrupting TSP-1 were investigated: the interaction of CD47 in human malignant melanoma A375 transplantation. In this model, the system management of TAX2 induces tumor necrosis by reducing tumor necrosis, and makes the tumor less invasive. In addition, TAX2 treatment also significantly inhibited B16F10 murine melanoma cells and metastasis in homologous experimental model of lung metastasis was analyzed histopathologically and longitudinal and quantitative transfer process proved by follow-up CT. In conclusion, through the combination of bioinformatics and preclinical studies, the results suggest that the targeting of TSP-1/ CD47 axis may represent a valuable therapeutic option for the treatment of melanoma [49].

Summary and Perspective

On the current study of TSP-1, the vast majority have recognized its regulatory and inhibition of the biological role of blood vessels. But the specific role of TSP-1 in tumor are some controversy and argument, as most of the current literature has said it has a negative regulatory role in growth inhibition of angiogenesis and tumor cells in the various tumors, but its action principle and mechanism remains to be seen, to sum up, it is not difficult to see on TSP-1 the research will undoubtedly give the development and prognosis of the tumor to bring new inspiration and guidance, and some scholars for exploring the [50]. TSP-1 may serve as a potential tumor suppressor gene, which may lead to a new starting point for the study of cancer.

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