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Research Progress of Gal-1 and Gastric Cancer

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Abstract

Gastric cancer (GC) is one of the most common cancers in the world and the leading cause of cancer-related death in China. At present, the intervention measures for GC are limited. Therefore, it is particularly important to find biological markers and targeted therapy for the occurrence and development of GC. Galectin-1 (Gal-1) is a member of the human lectin family and has attracted attention for its association with human tumor invasion behavior. Recent studies have found that the expression of Gal-1 in tumor cells is closely related to the migration, invasion and tumor-induced angiogenesis of tumor cells. This article reviews the research progress of Gal-1 in GC, which is helpful to discover the therapeutic effect of Gal-1 in GC diseases.

Keywords

Galectin-1, Gastric Cancer, Research Progress

1. Introduction

GC is one of the most lethal malignant tumors and the third leading cause of cancer-related death worldwide [1]. At present, some risk factors for gastric cancer have been identified, such as dietary carcinogens, Helicobacter pylori infection, and genetic factors, but primary prevention is still a daunting challenge for the public [2]. At present, the progress of tumor treatment has brought positive effects to the management of GC. However, because the early symptoms of GC are not obvious, most patients are on the verge of advanced stage when diagnosed and miss the opportunity of surgery, resulting in a 5-year survival rate of less than 5% [3]. Therefore, it is particularly important to clarify the biomarkers mediated by the formation and progression of GC. By understanding the process of GC, more effective treatment methods can be improved to improve the prognosis of patients.

The β-galactoside binding lectin family is galactose lectin. They have been found in multicellular organisms and can be detected both intracellularly and extracellularly. Galactose lectin is a soluble lectin family with affinity for β-galactoside-containing sugars. Galectins may be involved in the transition from healthy tissue to tumor or inflammatory tissue, and lead to the persistence of these pathological conditions through intracellular and extracellular mechanisms [4]. Galectins can also affect most processes of tumor progression and regulate resistance to a variety of anti-cancer treatments, including immunotherapy, chemotherapy, radiotherapy, targeted therapy and anti-angiogenesis therapy [5]. In addition, galectins may help amplify, maintain, or alleviate the regulatory circuits of tissue fibrosis and inflammation by selectively targeting different cell types and their microenvironments. Therefore, galectin has been proposed as a therapeutic target in a wide range of pathological conditions and is currently undergoing clinical evaluation.

Galectin-1 (Gal-1) encoded by the LGALS1 gene is a 14-kDa lectin belonging to the galactoside family. It is widely expressed in various immune cells and regulates the function of various immune cells. It promotes intercellular or intercellular extracellular communication by binding to ethylene glycol-coupled proteins on the cell surface [6] [7]. Cancer-associated fibroblasts (CAFs) produce Gal-1 through secretory and paracrine pathways. Gal-1 binds to the glycogen membrane receptor of tumor cells and regulates downstream signal transduction, thereby affecting tumor cell adhesion, migration, invasion, tumor-induced angiogenesis and apoptosis. In addition, Gal-1 regulates signal transduction and gene transcription by interacting with tumor cell surface or nuclear proteins, such as FOXP3 [8].

2. Gal-1 and Tumor Microenvironment

Tumor microenvironment (TME) is a complex functional environment, including extracellular matrix and various types of stromal cells, such as mesenchymal stem cells, macrophages, inflammatory cells and fibroblasts. Fibroblasts can be activated into CAF in the early stage of tumorigenesis and become the most abundant cell type in the tumor matrix. When CAFs are activated, a variety of proteins are highly expressed. At present, smooth muscle actin-α (SMA-α), which affects the movement of fibroblasts, is the most widely used CAF marker. Recent studies have shown that CAFs are highly activated in GC tissues and are closely related to the malignant potential of GC, such as tumor size, tumor invasion, metastasis, metabolism and remodeling [9]. Further studies have confirmed that CAFs promote the tumorigenesis, development, invasion, metastasis and other malignant potential of GC cells by secreting various cytokines acting on GC cells [10].

In TME, Gal-1 establishes a physical connection between the extracellular matrix and vascular endothelial cells, thereby acting as a scaffold for vascular network formation and vascular growth, providing physical support for the new vascular system [11]. Gal-1 is a multivalent carbohydrate binding protein that regulates the activity of malignant tumor cells by cross-linking glycoproteins in TME. Gal-1 is

synthesized on cytoplasmic ribosomes with a prototype acetylated N-terminus, but there is no signal peptide, and then Gal-1 is transported from the nucleus to the inner side of the cell membrane and secreted into the extracellular TME. In the extracellular environment, Gal-1 has a high affinity with β-galactoside and regulates the homotypic aggregation of cancer cells by interacting with glycoconjugates on the cell surface.

3. The Role of Gal-1 in GC

GC invasion and metastasis are very complex, involving many factors and steps. Gal-1 promotes GC metastasis by regulating adhesion molecules in the tumor matrix and interacting with immune-related pathways [12]. Due to its complexity and diversity, the molecular mechanism of Gal-1 action is still under study. To date, several studies have examined the expression of Gal-1 in GC and its potential prognostic significance. According to the existing research, we can know that Gal-1 is related to some related signaling pathways of GC.

3.1. Gal-1 and β (TGF-β1)/Sma and Mad-Related Protein (Smad) Pathway

Epithelial-mesenchymal transition (EMT)-mediated down-regulation of epithelial markers and up-regulation of mesenchymal markers play an important role in GC metastasis and invasion [13]. EMT induces loss of epithelial cell polarity, thereby reducing their contact with matrix and peripheral cells, and reducing intercellular interactions, thereby enhancing cell migration and movement. TGF-β is an important EMT inducer in the development process and pathological state. TGF-β stimulation of certain cultured epithelial cell lines can induce EMT. TGF-β-induced EMT can occur through the classic Sma and Mad-related protein (Smad) pathway or non-Smad pathway. TGF-β activates Smad2 and Smad3 and binds to Smad4 in the classic Smad pathway. The Smad complex is then transferred to the nucleus to mediate inhibition or activation of target genes and transcription factors. At the same time, the Smad complex also induces nuclear microRNA expression, thereby inhibiting the expression of characteristic proteins in epithelial cells and promoting the expression of proteins that give mesenchymal cell characteristics, thereby promoting EMT. Research shows [14], Gal-1 induces EMT by activating the TGF-β/Smad pathway and promotes GC invasion, metastasis and angiogenesis simulation.

3.2. Gal-1 and Hedgehog/GLI Signaling Pathway

Gal-1 can induce EMT by up-regulating Hedgehog (Hh) signal through glioma-associated oncogene-1 (GLI1) in GC. The Hh/GLI signaling pathway was first discovered in Drosophila and is controlled by two receptors on the target cell membrane: plaque (Ptc) and smooth (Smo). Ptc is composed of 12 transmembrane domains, which can directly bind to ligands and negatively regulate Hh signaling. Smo is a G protein-coupled transmembrane protein and an important receptor

for Hh signaling. The nuclear factors involved in Hh signal transduction include transcription factor Ci/GLI and so on. Under standard conditions, Ptc inhibits the activity of Smo protein, thereby inhibiting the downstream pathway. Classical Hh signal transduction involves the Ptc binding of Hh, relieves the inhibition of Smo, and promotes the entry of GLI protein into the nucleus and activates the transcription of downstream target genes. During embryogenesis, Hh/GLI signaling is activated and regulates cell proliferation and differentiation, while it remains silent in adults. However, excessive activation of Hh/GLI is associated with the carcinogenic effects of a variety of human malignancies, including GC [15]/GLI1 signal transduction is a promising target for cancer therapy because this pathway controls the main biological characteristics of cancer, including proliferation, metastasis, survival, self-renewal and angiogenesis. Studies have shown that the expression of GLI1 in GC tissues is significantly higher than that in matched non-cancerous tissues [16]. Intracellular Gal-1 is the main regulator of H-Ras nanoclusters. It is known that Ras signal transduction can induce or enhance the expression of Sonic Hedgehog (SHh). In GC, Gal-1 activates the Hh/GLI1 signaling pathway through Ras/SHh, and up-regulates the Hh signaling pathway through GLI1 in GC to induce EMT, thereby affecting the growth and evolution of cancer cells.

3.3. Gal-1 and NRP-1/c-JUN/Wee1 Pathway

Previous studies have shown that Gal-1 regulates cell proliferation and repair by interacting with NRP-1 receptors [17]. The c-JUN protein is a component of the activating protein-1 (AP-1) transcription complex and the most active transcription factor in the AP-1 complex. It can affect tumor proliferation, metastasis, differentiation and apoptosis [18]. Wee1 belongs to the cyclin-dependent protein kinase family. It binds to the terminal phosphorylation site and inactivates cyclin B, leading to cell cycle arrest in G2 phase cells in response to DNA damage. This process is closely related to drug resistance during tumor cell proliferation. C-JUN can bind to the Wee1 promoter to regulate the expression of Wee1 [19]. *In vitro* experiments of Zheng [20], rhGal-1 treatment significantly up-regulated the expression of NRP-1 receptor proteins c-JUN and Wee1. In addition, immunohistochemistry confirmed that Gal-1 was positively correlated with NRP-1/C-JUN/Wee1 in GC. At the same time, NRP-1 inhibitor inhibited Gal-1-induced GC cell proliferation and metastasis. Gal-1 can promote the proliferation and metastasis of GC cells by activating the NRP-1/c-JUN/Wee1 pathway.

4. The Therapeutic Potential of Gal-1

Gal-1 has potential value as a therapeutic target. The expression of Gal-1 in tumor tissues can be used as a biological modifier for tumor growth, invasion, angiogenesis and metastasis, thereby forming a tumor microenvironment that promotes tumorigenesis. These functions can decisively affect the patient's treatment response. Therefore, some reports have shown that Gal-1 can induce the resistance of some malignant tumors to specific treatments, such as the kinase inhibitor so-

rafenib in liver cancer. Many articles have analyzed Gal-1 inhibitors as a therapeutic tool for a variety of tumors [21]. For example, Gal-1 blockade significantly increases T cell infiltration in tumors, leading to a better response to anti-PD-1 therapy [22]. The specific efficacy of Gal-1 inhibitors has been reported in thyroid cancer, liver cancer, breast cancer or small cell lung cancer [23].

Gal-1 is associated with tumor growth and invasiveness of various tumor types, and is often expressed in the matrix and epithelial compartments of GC tissues. Studies have shown that [24], the potential of Gal-1 as a prognostic marker and therapeutic target for GC indicates the feasibility of developing targeted drugs for this protein to improve the prognosis of patients. It is proved that Gal-1 overexpression may become a cost-effective technique for targeted therapy in GC patients in the future. In GC, the expression of Gal-1 is closely related to tumor progression, immune escape and poor prognosis. In order to more accurately evaluate the prognosis of GC patients and achieve personalized treatment, combined detection of Gal-1 and other potential biomarkers may be of great significance. For example, Tregs are a class of T cells with immunosuppressive function, and their infiltration in the tumor microenvironment is associated with poor prognosis. Gal-1 enhances immunosuppression by promoting the function of Tregs. Detection of Gal-1 and Tregs levels can help to evaluate the immunosuppressive status of gastric cancer and guide immunomodulatory therapy. In the future, it is necessary to verify the combined application value of Gal-1 and these biomarkers through multi-omics analysis and clinical trials, so as to provide more accurate treatment options for GC patients.

However, Gal-1 targeted therapy may still have some potential side effects. For example, Gal-1 plays an important role in regulating immune tolerance and inhibiting inflammatory response. Inhibition of Gal-1 may lead to excessive activation of the immune system, triggering autoimmune diseases or inflammatory responses. Gal-1 plays a dual role in angiogenesis. It not only promotes tumor angiogenesis, but also participates in the angiogenesis of normal tissues. Inhibition of Gal-1 may affect the angiogenesis of normal tissues, resulting in tissue ischemia or delayed repair. On the mechanism of drug resistance, tumor cells may evade Gal-1 targeted therapy through various mechanisms. Gal-1 belongs to the galectin family, which has certain similarities in structure and function with other family members (such as Gal-3, Gal-9, etc.). When Gal-1 is inhibited, tumor cells may compensate for the loss of Gal-1 function by up-regulating Gal-3 or other family members, thereby maintaining tumor growth and immune escape. Secondly, the adaptability of the tumor microenvironment may change, and tumor cells may counteract the effect of Gal-1 inhibition by recruiting more immunosuppressive cells (such as myeloid-derived suppressor cells MDSCs) or up-regulating other immunosuppressive molecules (such as PD-L1, CTLA-4). In future studies, it may be possible to design highly specific inhibitors for Gal-1 to reduce the impact on other members of the galectin family, thereby reducing off-target effects, or to combine Gal-1 inhibitors with other therapies (such as immune checkpoint in-

hibitors, chemotherapy or radiotherapy) to overcome drug resistance and enhance anti-tumor effects.

5. Complimentary Close

At present, GC has a high morbidity and mortality worldwide. In this review, we summarize the role of Gal-1 in tumor progression, and the manipulation of the Gal-1 signaling pathway provides a new way to improve the results of checkpoint blockade immunotherapy. Gal-1 is widely distributed in the tumor microenvironment. How to accurately deliver the inhibitor to the tumor site and maintain the effective concentration is now a technical problem. In addition, because the body's immune reactivity and immune protection mechanisms may be affected by the level of Gal-1 and its ligands, it is necessary to emphasize the safety analysis of Gal-1 targeted therapy side effects. It is also necessary to clarify the targeting of Gal-1 and its ligands in tumors and immune tissues, multiple intervention plans, and the correct dose for *in vitro* analysis. Although there is no clinically approved Gal-1 targeting agent, convincing experimental and preclinical data support the definitive role of Gal-1 in cancer progression. However, due to its complexity and diversity, the molecular mechanism of Gal-1 action is still under further study, and more research is needed on the development of Gal-1 targeted therapy. Therefore, the application of Gal-1 targeting is worthy of attention.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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