

Advances in the Mechanism of Action of Gamma-Glutamyltransferase and Lactate Dehydrogenase in Colorectal Cancer

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Abstract

As the third most common malignant tumor in the world, colorectal cancer (CRC) poses a serious threat to human life and health with its high morbidity and mortality. Although early-stage patients can realize the possibility of cure through surgery, advanced-stage patients have a poor prognosis. Research has found that gamma-glutamyl transferase (GGT) and lactate dehydrogenase (LDH) are associated with the occurrence, development, and prognosis of colorectal cancer. Therefore, exploring their roles in the occurrence and development of colorectal malignancies can help identify new therapeutic targets for cancer treatment. This article reviews the relevant mechanisms of GGT and LDH in colorectal cancer.

Keywords

Colorectal Cancer, Gamma-Glutamyltransferase, Lactate Dehydrogenase, Mechanism of Action

1. Introduction

With the accelerated development of science and technology industrialization, people have undergone great changes in clothing, food, housing and transportation, and cancer has become one of the most frequent and common diseases affecting human health. Research data show [1] that the incidence and mortality rates of colorectal cancer ranked high in the world as the 3rd in terms of incidence, and the 2nd in terms of death, which suggests that colorectal cancer is not only the third most common type of gastrointestinal malignant tumors, but also the second most common form of cancer that leads to cancer-related deaths. Cur-

rently, the treatment of colorectal cancer is mainly based on surgical resection, supplemented by neoadjuvant or adjuvant therapies that help to improve the overall survival of colorectal cancer patients [2]. Despite the continuous optimization of treatment options for colorectal cancer, the survival rate of patients with tumor recurrence and metastasis is still low [3]. Moreover, the early symptoms of colorectal cancer are not typical, and most of them have progressed to advanced stages when diagnosed, resulting in unsatisfactory treatment outcomes for some patients. Therefore, in-depth study of the development mechanism and prognosis-related risk factors of colorectal cancer is of great significance for the early diagnosis and treatment of colorectal cancer and improvement of patients' prognosis.

The formation and development of malignant tumors is the result of a variety of factors, involving the participation of a variety of mechanisms, mainly including: long-term inflammatory stimulation, cellular gene mutation, tumor angiogenesis, promotion of cell proliferation and immune escape and other mechanisms. It has been pointed out [4] that chronic inflammation is a hallmark of cancer, such as inflammatory bowel disease, hepatitis, chronic atrophic gastritis, etc. are considered to be closely related to cancer development. Colorectal cancer is one of the best examples of tumors strongly associated with chronic inflammation. Meanwhile, more and more studies have shown that inflammation can be involved in tumorigenesis and development by damaging DNA, affecting oncogenes, and promoting cell proliferation and metastasis [5]. And inflammatory markers such as γ -glutamyltransferase and lactate dehydrogenase, as the intrinsic manifestation of inflammatory response in the organism, are involved in the process of colorectal cancer development, which provides a new research direction in terms of diagnosis and prognosis prediction of colorectal cancer. In this paper, we review the mechanism of γ -glutamyltransferase (GGT) and lactate dehydrogenase (LDH) in colorectal cancer.

2. Role of Gamma-Glutamyltransferase in Colorectal Cancer

2.1. Biological Properties of Gamma-Glutamyltransferase

Gamma-glutamyltransferase (GGT) is an extracellular enzyme anchored to the cytoplasmic membrane that transfers γ -glutamyl groups from GSH and other γ -glutamyl compounds to amino acids or dipeptides and contributes to the metabolism of glutathione [6]. Glutathione plays an important role in protecting cells from oxidative stress and maintaining the redox state. GGT degrades extracellular GSH to produce cysteinylglycine and glutamate, which are hydrolyzed by cell-surface dipeptidyl peptidases to produce glycine and cysteine, and the amino acids produced by these degradations are reutilized to participate in intracellular GSH synthesis [7], playing a key role in the maintenance of GSH homeostasis and the defense against organismal GGT activity is widely used as an indicator for assessing liver function, but recent epidemiologic studies have found that elevated levels of GGT activity are associated with an increased risk of developing a variety

of diseases, such as cardiovascular disease, metabolic disease, and cancer [8]-[10]. In a case-control study [11], GGT was found to be an independent risk factor for colorectal adenomas or cancers and could be used for early detection of colorectal adenomas/cancers. A meta-analysis found [12] that higher GGT levels were associated with a higher incidence of several gastrointestinal cancers, including colorectal cancer. This is consistent with the findings of Hong *et al.* [13]. Therefore, it is important to explore the mechanism of GGT in colorectal cancer for the prevention and treatment of CRC.

2.2. Mechanism of Action of GGT in Colorectal Cancer

GGT may play an important role in the proliferation and metastasis of colorectal cancer cells. A large number of studies have shown that oxidative stress is the main mechanism of colorectal cancer development. On the one hand, it can increase the cell mutation rate leading to cell cancer. On the other hand, oxygen free radicals (ROS) induced by oxidative stress activate the NF- κ B pathway, stimulating the production of pro-inflammatory cytokines (TNF α , IL-1 β , IL-6) and inflammatory mediators (COX-2), which drive inflammatory responses. This leads to chronic inflammation in intestinal epithelium, increasing the risk of cell carcinogenesis. Moreover, the continuous activation of NF- κ B also contributes to tumor formation [14]. Moreover, excessive ROS can damage the DNA of colonic epithelial cells, leading to the emergence of relevant oncogene mutations and genomic instability, and ultimately promoting excessive cell proliferation and carcinogenesis [15]. As an alternative biomarker of oxidative stress, the role of GGT in colorectal cancer should not be ignored. Research has shown that [16] GGT possesses both antioxidant and pro-oxidant activities, which are normally in equilibrium. However, in cells overexpressing GGT and in the presence of redox catalysts (such as iron or copper), its pro-oxidant activity dominates in the cellular microenvironment, leading to chain pro-oxidant reactions and generating reactive oxygen species (ROS). Excessive ROS can cause oxidative DNA damage and genomic instability, which are precursors to carcinogenesis [17]. In addition, elevated ROS levels also activate the NF- κ B and mitogen-activated protein kinase (MAPK) pathways, which produce pro-inflammatory cytokines and inflammatory mediators, inducing inflammatory responses and cell proliferation. Not only that, up-regulation of GGT expression can protect cancer cells from oxidative stress by increasing intracellular GSH levels, thus supporting their growth and survival [18]. The most important point is that GGT can induce tumor angiogenesis by increasing intracellular reactive oxygen species (ROS) levels, activating the hypoxia-inducible factor-1 α (HIF-1 α) signaling pathway to stimulate the secretion of vascular endothelial growth factor (VEGF), thereby providing vascular conditions for tumor cell migration and accelerating cancer cell growth, migration, and invasion [19]. It has been reported in the literature [20] that tumors with high GGT expression can also develop resistance to pro-oxidant chemotherapeutic agents, which may be related to the disruption of the regulation of the redox-sen-

sitive transcription factor Nrf2 in CRC [21].

A number of studies have demonstrated that in colorectal cancer, high levels of GGT are significantly associated with a poorer prognosis. Patients with high GGT levels have a higher risk of developing advanced colorectal adenomas compared to those with low GGT levels [22]. In colorectal cancer liver metastases, most patients with metastases had increased serum GGT levels, while patients without metastases had low serum GGT levels [23]. It is inferred that GGT levels are important in both the growth and invasive stages of cancer cells and have the potential to be a biomarker of carcinogenesis and tumor progression.

3. Mechanism of Action of Lactate Dehydrogenase in Colorectal Cancer

3.1. Biological Properties of Lactate Dehydrogenase

Lactate dehydrogenase (LDH) is a key enzyme involved in glycolysis, converting pyruvate to lactate under hypoxic conditions while generating ATP to provide energy for the cell. In normal cells, LDH exists in a variety of isoenzymes, and the expression and function of different isoenzymes vary in different tissues. When cells are damaged, LDH is released into the blood. Therefore, elevated serum LDH exists in many clinical situations, such as severe infections, cancer, heart disease, and liver disease [24]. In tumor cells, due to their highly active glycolytic metabolism and the higher affinity of LDHA for pyruvate [25], the expression and activity of LDHA are usually significantly increased in cancer cells, suggesting that LDH may be a potential diagnostic marker for cancer. Moreover, even under aerobic conditions, LDHA can metabolize pyruvate into lactate and ATP, providing energy for cancer cell growth and proliferation, and promoting tumor development. This is the famous Warburg effect [26]. In recent years, clinical studies have found that LDH level has been proved to be an important prognostic marker for a variety of solid tumors, including colorectal cancer, and the literature has reported [27] that the LDH level correlates with tumor load, which may reflect tumor growth and invasive potential. Jinxia Gao *et al.* [28] found that in colorectal cancer, patients with LDH-5 positivity had a poor prognosis, which may be due to the fact that LDH-5 positivity has a pro-carcinogenic effect and enhances tumor cell invasiveness. Gao Ce *et al.* [29] concluded that LDH levels were elevated in colorectal cancer patients and correlated with clinical stage, lymph node metastasis and degree of differentiation. This suggests that elevated LDH levels are an unfavorable indicator of survival in cancer patients and can be used as a marker of tumor aggressiveness. Therefore, exploring the mechanism of LDH in colorectal cancer is expected to be a new target for tumor therapy.

3.2. Mechanism of Action of LDH in Colorectal Cancer

LDH also plays an important role in colorectal cancer invasion and metastasis. It has been found that LDH is involved in the reprogramming of tumor energy metabolism, and its overexpression leads to vigorous glucose metabolism in tumor

cells, and large amounts of lactate efflux lead to acidification of the tumor micro-environment, which hinders the proliferation and function of CD8⁺ T cells, and at the same time inhibits the function and survival of T and NK cells, suppresses the anti-tumor immune response, and promotes the proliferation and invasion of cancer cells [30] [31]. Meanwhile, high levels of LDH can induce tumor angiogenesis [32]. In a mouse model study by Frédérique Végran [33] *et al.* it was found that lactate can enter endothelial cells via the monocarboxylic acid transporter protein MCT-1, triggering phosphorylation/degradation of I κ B α , which then stimulates the autocrine NF- κ B/IL-8 (CXCL8) pathway driving cell migration and angiogenesis. In addition, it has also been found [34] that high expression of LDH5 in cancer cells can activate multiple signaling pathways such as the HIF-1 α pathway and VEGF/VEGFR2 to increase the expression of pro-angiogenic factors such as HIF-1 α , pKDR, VEGFA, PDHK, etc., which induces the formation of tumor blood vessels, provides more nutrients and oxygen for tumor growth, and creates favorable conditions for colorectal cancer growth, invasion and metastasis.

Numerous studies have shown that LDH can be used as one of the indicators of poor prognosis in colorectal cancer patients. It has been pointed out [35] that in patients with colorectal cancer liver metastases (CRLM), the overall survival of patients with elevated LDH is lower than that of patients with reduced LDH, and it is an independent risk factor for the prognosis of patients with CRLM. Some studies by Hai *et al.* [36] have found that the expression of LDH-A in CRC tumor cells is significantly higher than that of normal cells, and that such a high level of expression is correlated with a poorer survival rate. Therefore, LDH has great research potential and value in colorectal cancer development and prediction of prognosis.

4. Summary and Outlook

In summary, GGT promotes tumor cell proliferation and metastasis by regulating glutathione metabolism and oxidative stress balance. For example, in the early stages of colorectal cancer, increased GGT activity may help tumor cells avoid oxidative stress damage and promote their growth. In advanced and metastatic stages, its high expression can promote tumor invasion and spread, as well as resistance to chemotherapy drugs. LDH not only mediates aerobic glycolysis to provide energy for CRC cells but also accelerates tumor invasion and progression by acidifying the tumor microenvironment and inducing tumor angiogenesis. Notably, LDH levels often significantly increase in advanced and metastatic colorectal cancer, reflecting not only the tumor's growth potential and invasiveness but also closely correlating with metastatic burden, serving as a poor prognostic indicator in advanced patients. Therefore, In-depth study of the mechanisms of GGT and LDH in different stages (such as early, advanced, and metastatic) of colorectal cancer development can reveal their biological functions in tumor formation and progression, highlight their value as prognostic markers, which helps in early diagnosis and efficient identification of patients with poor prognosis, optimizes treat-

ment plans to improve prognosis, and enhances patients' quality of life and survival. The most distinctive feature is the development of specific inhibitors targeting GGT and LDH, such as gossypol and FX11 as LDHA inhibitors, which can inhibit the formation of lactic acid and ATP, thereby achieving anti-tumor effects and providing new targeted therapy strategies for colorectal cancer treatment. However, due to the adverse reactions and non-specific characteristics of these inhibitors, there are still no specific LDHA or GGT inhibitors applied in clinical practice at present. Therefore, more clinical studies are needed to explore. It is hoped that in the future, through the research on GGT and LDH in colorectal cancer, new methods can be explored for the diagnosis, treatment and prognosis evaluation of CRC.

Conflicts of Interest

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

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