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EDITORIAL

Six transmembrane epithelial antigens of the prostate to illustrate inflammatory response in gastrointestinal cancers

Yi-Han Wu, Lian-Xiang Luo

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Abstract

Gastrointestinal cancer (GIC) is a common and widespread form of tumor, with colonoscopy and upper gastrointestinal endoscopy available to detect relevant precancerous polyps and lesions. However, many patients are already in the late stages when first diagnosed with such cancer, resulting in a poor prognosis. Thus, it is necessary to explore new methods and research directions in order to improve the treatment of GIC. Given the specific nature of the gastrointestinal tract, research should focus on the mechanisms of various inflammations and the interactions between food entering and exiting from the gastrointestinal tract and cancer cells. Interestingly, six transmembrane epithelial antigens of the prostates (STEAPs) have been found to be significantly linked to the progression of malignant tumors, associated with intracellular oxidative stress and playing a major role in inflammation with their structure and function. This paper explores the mechanism of STEAPs in the inflammatory response of GIC, providing a theoretical basis for the prevention and early intervention of GIC. The basic properties of the STEAP family as metal reductase are also explained. When it comes to intervention for GIC prevention, STEAPs can affect the activity of Fe^{3+}, Cu^{2+} reductase and regulate metal ion uptake *in vivo*, participating in inflammation-related iron and copper homeostasis. Thus, the mechanism of STEAPs on inflammation is of important value in the prevention of GIC.

Key Words: Six transmembrane epithelial antigens of the prostate; Gastrointestinal cancer; Inflammation; Gastric cancer; Colorectal cancer; Hepatocellular carcinoma

Core Tip: Six transmembrane epithelial antigens of the prostate (STEAPs), a family of metal reductases, are associated with intracellular oxidative stress and an inflammatory reaction, while chronic inflammation has been linked to an increased risk of gastrointestinal cancers (GICs). This review of STEAPs offers a theoretical foundation for diagnosis and treatment approaches for GIC patients.

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INTRODUCTION

Numerous research findings demonstrate that inflammation is an essential element of tumor progression. Infection and chronic inflammatory stimulation are associated with the tumorigenesis of gastric cancer (GC), colorectal cancer (CRC), hepatocellular carcinoma (HCC) and other gastrointestinal cancers (GICs)[1]. Furthermore, the tumor microenvironment is a prerequisite for the tumorigenesis, which is largely controlled by inflammatory cells[2]. Clinical trials show that about 15% of cancer patients have infection, chronic inflammation or autoimmune diseases in the same tissue or organ before the cancer occur, implying that precancerous inflammation exists before the growth of a tumor. The most prominent relationship between inflammation and malignant tumors is observed in CRC patients with inflammatory bowel disease (such as chronic ulcerative colitis and Crohn's disease), hepatitis patients who are predisposed to liver cancer, and chronic *Helicobacter pylori* (*H. pylori*) infection, a critical risk factor for GC[3]. GC, as one of the most common malignancies in humans, is mainly caused by sustained *H. pylori* infection[4], which requires iron to promote bacterial growth[5].

THE INFLUENCE OF IRON ENVIRONMENT ON THE BACTERIAL FLORA

In an iron deficiency environment, *H. pylori* can maintain its growth by binding to hemoglobin, transferrin and lactoferrin and extracting iron from it. This phenomenon is very significant in iron-free transferrin and lactoferrin, which limits its ability to obtain iron from conventional serum[6]. It was revealed that both TfR and ferritin light chain were overexpressed in all *H. pylori* positive tissues, verifying the role of iron acquisition-related genes *H. pylori* connected to the gastric mucosa. In addition, colonization by *H. pylori* can lead to high production of reactive oxygen species (ROS), which necessitates the usage of multiple strategies to reduce the detrimental effects of ROS. Unfortunately, overabundance of ROS can cause chronic inflammation and cell damage, which is a main factor for GC[7].

SIX TRANSMEMBRANE EPITHELIAL ANTIGENS OF THE PROSTATE AND IRON/COPPER HOMEOSTASIS

Studies have indicated the potential of six transmembrane epithelial antigens of the prostate (STEAPs) in *H. pylori*-associated GC inflammatory response. Moreover, STEAP4 was found to be highly expressed in GC tissues, which is linked to the late clinical stage and poor prognosis of GC patients. The expression of STEAP4 is positively correlated with the infiltration of B cells, CD4+ T cells, macrophages, neutrophils and dendritic cells, suggesting that it may be involved in the regulation of tumor microenvironment[8].

The STEAP family consists of four structurally similar members, namely STEAP1, STEAP2, STEAP3 and STEAP4[9], typically acting as an oxidoreductase involved in the absorption and reduction of iron and copper, with their location on the cell membrane as a transmembrane protein. Thus, STEAP can be used to regulate iron homeostasis to avert chronic *H. pylori* infection and prevent the occurrence of GC. Besides the wide expression of STEAP1 and the co-localization of transferrin to control iron homeostasis, STEAP2-4 can reduce Fe^{3+} and Cu^{2+} and enhance the intake of iron and copper within the cells[10].

The gastrointestinal tract is the primary organ for absorbing copper, a vital micronutrient and cofactor for essential copper-dependent enzymes. When pathogens enter the host, the increased copper concentration will trigger a variety of reactions[11]. According to oligonucleotide microarray analysis of genes related to copper homeostasis, STEAP3 was found to be heightened in CRC, potentially indicating a connection to copper accumulation[12]. Even under the condition of iron deficiency, overexpression of STEAP3 can increase iron storage and thus produce resistance to apoptosis induced by iron deficiency[13]. In contrast to the other STEAP family members, STEAP4 expression is lower in CRC tissues than in normal tissues, and its expression is positively associated with immune infiltration and immune-related biomarkers[14]. Xue *et al*[15] using the colitis-associated colon cancer model, found that the mitochondrial iron imbalance associated with high STEAP4 levels is the key mechanism of inflammation affecting colon tumorigenesis, suggesting that STEAP4 is an important regulator of inflammatory response. In colitis-associated tumorigenesis model, pro-inflammatory cytokine interleukin-17 can also mobilize copper metabolism by inducing copper uptake by STEAP4-dependent cells, which is

essential for the formation of colon tumors[16]. In HCC, serum copper concentration has been proved to be an auxiliary monitoring index for the diagnosis, prognosis and follow-up of chronic liver disease[17,18]. So far, the role of STEAP3 in regulating copper homeostasis in GIC has been confirmed.

It has been established that the STEAP family plays the role of metal reductase in the regulation of iron/copper homeostasis in inflammation-related CRC formation and development in different GIC diseases. Additionally, STEAP4 has been found to have a role in controlling inflammation, fatty acid metabolism and glucose metabolism[19-21]. Pathological studies have confirmed the involvement of STEAP1-3 in the development of GC. Although there is little information on the role of these proteins in inflammatory response, it is plausible that they may serve a similar purpose. Currently, STEAPs are being investigated as a potential strategy to prevent and treat GIC. This approach combines microbiology, pharmacology, and pathology to explore novel treatments for GIC patients. As the transport mechanism of STEAPs and their involvement in cancer progression are being studied, the prospects for GIC treatment are promising.

ROS

ROS and reactive nitrogen, produced by inflammatory cells, can lead to oxidative damage of DNA in gastrointestinal cells, which can activate oncogenes and/or deactivate tumor suppressor genes. Moreover, epigenetic alterations that promote the development of GIC can be induced. Therefore, molecules that can influence cell survival or inflammation may be effective in treating GIC. With the increasing use of STEAPs as a cancer target, more inflammation-based treatments for GIC are likely to be explored in the future, particularly those involving STEAP family proteins.

CONCLUSION

The editorial states that STEAPs classes with similar structural components that act as metal oxidoreductases involved in various cellular activities, such as iron/copper absorption, inflammatory response, glucose and fatty acid metabolism, and oxidative stress control, the editorial notes. Moreover, STEAP expression is irregular in different cancers and is associated with the proliferation, migration, invasion, and metastasis of cancer cells, either promoting or suppressing cancer.

FOOTNOTES

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