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LETTER TO THE EDITOR

Leukocyte immunoglobulin-like receptor B2: A promising biomarker for colorectal cancer

Wen-Zhuo Zhao, Hong-Gang Wang, Xiao-Zhong Yang

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Abstract

According to the latest global cancer statistics, colorectal cancer (CRC) has emerged as the third most prevalent malignant tumor across the globe. In recent decades, the medical field has implemented several levels of CRC screening tests, encompassing fecal tests, endoscopic examinations, radiological examinations and blood tests. Previous studies have shown that leukocyte immunoglobulin-like receptor B2 (LILRB2) is involved in inhibiting immune cell function, immune evasion, and promoting tumor progression in acute myeloid leukemia and non-small cell lung cancer. However, its interaction with CRC has not been reported yet. Recently, a study published in the *World Journal of Gastroenterology* revealed that LILRB2 and its ligand, angiopoietin-like protein 2, are markedly overexpressed in CRC. This overexpression is closely linked to tumor progression and is indicative of a poor prognosis. The study highlights the potential of utilizing the concentration of LILRB2 in serum as a promising biomarker for tumors. However, there is still room for discussion regarding the data processing and analysis in this research.

Key Words: Colorectal cancer; Leukocyte immunoglobulin-like receptor B2; Angiopoietin-like protein 2; Therapeutic target; Noninvasive screening biomarker

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Core Tip: In this study, it has been extensively demonstrated that there is an overexpression of leukocyte immunoglobulin-like receptor B2 (LILRB2) and its ligand angiopoietin-like protein 2 in colorectal cancer tissues. Furthermore, these proteins have been found to be closely associated with tumor progression and poor prognosis. The author conducted an analysis of LILRB2 serum concentration using 313 serum samples and compared its advantages and disadvantages with traditional tumor markers such as carcinoembryonic antigen and carbohydrate antigen 199. However, we believe that certain aspects of data collection and analysis in the article warrant further consideration. Therefore, we would like to discuss our perspective on this intriguing research.

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TO THE EDITOR

According to the most recent global cancer statistics, colorectal cancer (CRC) is now the third most common malignant tumor worldwide. It has a notably high incidence rate, a poor prognosis at advanced stages, and ranks as the second leading cause of cancer-related deaths[1,2]. However, the implementation of population-based CRC screening, such as fecal occult blood tests and endoscopy, has significantly improved overall survival rates and brought about promising prospects for the cure of CRC[3]. We have carefully read the case-control study written by Wang *et al*[4]. This study commences by introducing the worldwide incidence and prognosis of CRC while emphasizing the challenges associated with its current treatment. Subsequently, the research team discovered the leukocyte immunoglobulin-like receptor B2 (LILRB2) protein through prior proteomic investigations[5]. The study postulates that LILRB2 could potentially serve as both a therapeutic target and a screening biomarker for CRC. Within the experimental section, the research team collected pathological specimens and medical records from a substantial number of patients who had undergone curative surgery for CRC. The expression levels of LILRB2 were compared across various populations using serological tests, immunohistochemistry, enzyme-linked immunosorbent assay, and other experimental methods. They also compared the differences in detection between this tumor marker and traditional tumor markers. Lastly, the study summarizes the experimental results and offers recommendations for further comprehensive research.

This study employed an innovative flow cytometry analysis method in combination with traditional immunohistochemical staining methods to mutually validate the results obtained from both approaches. This approach effectively confirms the reliability of the experimental findings. Moreover, the research team utilized gene platforms for online analysis of differentially expressed genes or mRNAs between normal and cancer tissues, which complemented the protein-level experiments. The team compared the expression levels of the LILRB2 protein in CRC tissues and adjacent tissues. They also analyzed the correlation between LILRB2 mRNA expression and angiopoietin-like protein 2 (ANGPTL2) mRNA expression in CRC tissues, as well as the correlation between LILRB2 protein expression and ANGPTL2 protein expression. Furthermore, they compared the diagnostic efficiency of LILRB2 with traditional tumor markers (carcinoembryonic antigen and carbohydrate antigen 199) using serum samples.

We would like to congratulate the research team on their compelling findings. They conducted a comprehensive investigation into the expression changes of the LILRB2 protein and its ligand ANGPTL2 in the occurrence and development of colorectal tumors. However, there are some questions that require further consideration by the researchers regarding this article.

The researchers collected a total of 313 serum samples between February 2021 and October 2022. Among these, there were 117 preoperative serum samples from CRC patients, 85 postoperative serum samples, 93 serum samples from adenoma patients, and 18 serum samples from healthy controls. They then compared the differences in serum LILRB2 concentrations among CRC patients, adenoma patients, and healthy controls, and discovered statistically significant variations in LILRB2 concentrations among the three groups. However, we would like to point out that there is a significant disparity in the number of serum samples between the CRC patient group (202 samples) and the healthy control group (18 samples). This raises concerns about potential data bias in the research results. Additionally, the criteria for including patients with normal colonoscopy findings in the healthy control group may be too broad. We believe it is necessary to establish detailed inclusion criteria for the healthy control group.

It is intriguing that the research findings in this article suggest that LILRB2 mRNA expression does not correlate with overall survival or progression-free survival in CRC patients. However, the overexpression of the LILRB2 protein is significantly associated with reduced overall survival, indicating a poor prognosis in CRC patients and suggesting a pro-cancer role of the LILRB2 protein in CRC progression. These results warrant further in-depth studies to elucidate the mechanisms behind these intriguing findings.

During our review of the research results in the article, we noticed the absence of any mention regarding baseline data processing for the participants' data. This omission raises concerns about the potential introduction of bias into the research results, which could impact the accurate assessment of the findings and diminish the reliability and validity of the study.

Previous studies on LILRB2 have primarily focused on hematopoietic stem cells and bone marrow immune cells, with limited attention given to CRC. LILRB2 has been found to play a significant role in inflammatory response and cell proliferation processes in these cells[6,7]. However, LILRB2 enrichment has also been observed in several malignant tumors, such as acute myeloid leukemia, chronic lymphocytic leukemia, esophageal cancer, pancreatic cancer, non-small cell lung cancer, and breast cancer[8]. It is premature to consider LILRB2 as a specific tumor marker for CRC since elevated serum levels of LILRB2 can occur in various solid tumors. Additionally, the differential effects of LILRB2 mRNA and protein expression on CRC prognosis warrant further investigation. Moreover, LILRB2 inhibitors are currently in phase I clinical trials[9], and their efficacy in treating CRC requires further observation.

This study offers preliminary evidence supporting the potential of the LILRB2 protein as a novel therapeutic target and non-invasive screening biomarker for CRC. Its implications are particularly beneficial for clinical practitioners, as it enables early screening, precise treatment and accurate prognostic evaluation of CRC.

FOOTNOTES

Author contributions: Zhao WZ wrote the letter; Wang HG revised the letter; and Yang XZ contributed to the study design, manuscript revision, supervision of the study.

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