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EDITORIAL

Mechanisms and potential applications of COPS6 in pan-cancer therapy

Tong Wu, Miao-Rong Ji, Lian-Xiang Luo

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Abstract

The COP9 signalosome subunit 6 (COPS6) is abnormally overexpressed in many malignancies, yet its precise role in carcinogenesis is unknown. To gain a better understanding of COPS6's role, the authors conducted a pan-cancer analysis using various bioinformatics techniques such as differential expression patterns, prognostic value, gene mutations, immune infiltration, correlation analysis, and functional enrichment assessment. Results showed that COPS6 was highly correlated with prognosis, immune cell infiltration level, tumor mutation burden, and microsatellite instability in patients with a range of tumor types. This suggests that COPS6 may be a potential target for cancer treatment. Overall, this research provides insight into COPS6's role in cancer development and its potential therapeutic applications.

Key Words: COPS6; Biomarker; Tumor mutational burden; Immune infiltration; Prognostic analysis

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Core Tip: COPS6 expression is often increased in malignancies, and this is associated with a poor prognosis, suggesting that it could be a potential biomarker for tumors. However, the exact role of COPS6 in different types of tumors is still unknown. This research seeks to investigate the expression of COPS6 in various tumor tissues, its prognostic value, mutations in the gene, and the correlation between expression levels and immune infiltration with different types of immune cells.

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INTRODUCTION

According to World Health Organization, cancer is the second biggest killer of people all around the world. While mortality due to cancer has been on a decreasing trend in recent times, the mortality rates for lung, colorectal, and female breast cancer are still increasing, proving to be an immense challenge for medical professionals attempting to treat it[1,2]. With the increasing number of cancer treatments, including chemo, radiation, surgery, and immunotherapy, many cancer patients still have a poor prognosis or treatment outcome. This makes it imperative to look for new targets for early diagnosis and tailored treatment. COP9 signalosome (CSN) has been found to be involved in a range of processes, such as protein degradation, DNA repair, cell cycle control, signal transduction, transcriptional activation, and tumorigenesis[3]. COPS6 is responsible for maintaining the structural integrity and function of the CSN complex in an MPN domain-dependent manner[4,5].Recently, COPS6 has been a subject of intense research as it has been observed to facilitate the growth of various types of cancers. In mouse experiments, COPS6 was determined to increase tumor growth by decreasing the ubiquitination of Myc and enhancing the degradation of Fbxw7. Additionally, it was seen to inhibit the P53-mediated tumor suppression by stabilizing MDM2 protein[6,7]. COPS6 has been identified to be involved in the epithelial-mesenchymal transition process in various tumors, which can lead to invasion and metastasis. For instance, the COPS6-UBR5-CDK9 axis has been found to regulate melanoma proliferation and metastasis[8]. COPS6 regulates tissue protease L expression levels through the autophagy-lysosome system, thereby promoting cervical cancer cell migration and invasion[9].

The use of multi-omics analysis has been a hot topic in tumor research in recent years. In our recently accepted paper, the authors used publicly available databases to investigate the role of COPS6 in various types of cancers, such as cervical cancer, papillary thyroid cancer, colorectal cancer, breast cancer, lung adenocarcinoma (LUAD), and glioblastoma. Our analysis included an examination of the differential expression patterns, prognostic value, gene mutations, immune penetration, correlation analyses, and functionally rich assessments of COPS6. Our findings provide initial evidence of the potential of COPS6 in cancer treatment. Several studies have used multi-omics analysis to identify targets for the treatment of LUAD in addition to anti-programmed cell death protein 1/programmed cell death ligand-1 immune checkpoints. For example, using multi-omics analysis, it was found that the catalytically active gene immunomodulatory factor TIM3, selective polyadenylation associated with mRNA maturation has a risk correlation to the immune microenvironment, biological transcription, and tumor cell resistance in lung adenocarcinoma, which affects the survival and prognosis of lung adenocarcinoma patients[10,11]. The multi-omics analysis of COPS6 and lung adenocarcinoma deserves to be investigated in depth.

The authors used R programming to analyze The Cancer Genome Atlas data and found that COPS6 expression levels were higher in hepatocellular carcinoma and renal clear cell carcinoma tissues. Further analysis of the Clinical Proteomic Tumor Analysis Consortium database, GEPIA2 website, and other websites revealed that COPS6 expression was correlated with the clinical stage of LUAD, KICH, KRIP, and LIHC. Prognostic analysis showed that, while high COPS6 expression usually indicated a poor prognosis in most tumors, it was associated with a good prognosis in KRIP, BRCA, LUSC, and PCPG.

Genetic mutations are known to be a major contributor to tumor growth. Studies of related websites and databases have revealed that missense mutations are the most common type of COPS6 mutations, with the highest frequency being found in esophageal adenocarcinoma, although they do not significantly influence the prognosis of the tumor. The progression and prognosis of esophageal adenocarcinoma and bladder cancer correlate with lncRNAs, and whether cops6 can improve the prognosis of esophageal and bladder cancers by affecting lncRNAs needs to be further investigated[12,13]. Tumor mutational load (TMB) has become a popular biomarker for immunotherapy, which is the total number of mutations present in a tumor sample. The higher the TMB, the more neoantigens are present, increasing the chances that some of the neoantigens presented by MHC proteins will be immunogenic, thus triggering a T-cell response and eliminating the cancer cells[14]. COPS6 expression levels have been seen to be linked to an increase in TMB and microsatellite instability in different types of tumors. The tumor microenvironment is composed of immune cells like T and B lymphocytes, natural killer cells, and tumor-associated macrophages, which are essential in determining the abnormal functioning of the tissue and in the progression of malignant tumors[15]. COPS6 expression has been found to affect the immune microenvironment in various types of tumors, particularly in breast cancer. It has been observed that COPS6 is a mediator of IL-6 production in the tumor microenvironment and a suppressor of CD8+ T cell tumor infiltration[16]. Research in the given paper found that the expression levels of COPS6 had a negative correlation with infiltration of CD8+ T-cells, a weak correlation with natural killer-cell infiltration, and a varying relationship with macrophage infiltration, depending on the subtype. Furthermore, correlation and enrichment analysis of COPS6 revealed that GPS1 and TCEB2 had the strongest correlation with it, implying that it could serve as a cancer biomarker and provide new insight into its molecular mechanism and potential targeted treatments. Additionally, as there is a lack of research on the role of COPS6 beyond pan-cancer, the value of lopinavir/ritonavir (LPV/r) in the treatment of SARS, MERS, and COVID-19 is instructive for a broad exploration of the role of COPS6[17].

This research provides a comprehensive analysis of COPS6 in a variety of cancers using R software and online analytical databases. The results showed that COPS6 is highly expressed in most cancers and linked to high-risk features, suggesting that it could be a potential cancer biomarker. Additionally, correlation and enrichment analyses identified two genes, GPS1 and TCEB2, associated with COPS6, which could be further explored to understand its mechanisms. Furthermore, the study revealed the effect of COPS6 on the infiltration of immune cells in different tumors, providing new insights for potential immunotherapy applications. However, further experiments are needed to validate the findings of this study.

CONCLUSION

This study is the first to investigate the role of COPS6 in pan-cancer. Results showed that COPS6 is highly expressed in many cancer types and is usually associated with a worse prognosis. Additionally, there was variability in the correlation between COPS6 expression and cancer-associated fibroblast infiltration. Furthermore, COPS6 was found to inhibit CD8+ T-cell infiltration in the tumor microenvironment, which facilitates tumor immune escape. In terms of gene expression, GPS1 and TCEB2 were significantly linked to COPS6. However, further research is needed to validate these findings as this study only used bioinformatics analysis. In conclusion, this paper provides a theoretical basis for the potential use of COPS6 as a biomarker in cancer research.

FOOTNOTES

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