

# World Journal of *Gastrointestinal Oncology*

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## ABOUT COVER

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The primary aim of *World Journal of Gastrointestinal Oncology* (WJGO, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

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## Insight on BRAF<sup>V600E</sup> mutated colorectal cancer immune microenvironment

Hassan Mohammed Abushukair, Sara Mu'amar Zaitoun, Anwaar Saeed

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### Abstract

Colorectal cancer (CRC) is the second deadliest malignancy for both sexes. The BRAF<sup>V600E</sup> mutation, one of the most common driver mutations in CRC, is known for its poor prognosis due to the increased risk of metastasis. The effect of the BRAF<sup>V600E</sup> mutation on the tumor microenvironment was the topic of the study reported in *World Journal of Gastrointestinal Oncology*, with special focus on immune status. The authors presented insightful findings that were exclusively based on macrophage polarity and cytokine levels, without investigating other relevant immune elements. A more comprehensive look into the dynamic immune activity of cancer environments will warrant more meaningful practical findings. In this letter, we discuss other significant immune factors and their possible implications on the tumor microenvironment of BRAF-mutated CRC.

**Key Words:** Colorectal cancer; BRAF<sup>V600E</sup>; Tumor microenvironment; Microsatellite instability; Macrophages; Immune checkpoint proteins

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**Core Tip:** The immune landscape of the tumor microenvironment is a crucial indicator of the proliferative and invasive activity of the tumor cells and serves as a predictor of response to targeted immunotherapeutic modalities. BRAF<sup>V600E</sup> is one of the most common driver mutations in colorectal cancer thought to have a unique impact on the tumor immune microenvironment. It is unknown whether this impact is of a suppressive or activating nature. Future studies on larger samples, considering a wider array of immune elements, such as the infiltration of relevant immune cells as well as immune checkpoints' expression, are needed.

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## TO THE EDITOR

We read the interesting study by Zhi *et al*[1] on the immune status of BRAF<sup>V600E</sup>-mutated colorectal cancer (CRC), titled "BRAF<sup>V600E</sup> mutant colorectal cancer cells mediate local immunosuppressive microenvironment through exosomal long noncoding RNAs", in which they utilized patient tissue samples, CRC cell lines as well as in silico analysis to study correlations between the BRAF<sup>V600E</sup> mutation and changes in the local immune microenvironment of CRC. The authors reported an immunosuppressive microenvironment induced by exosomal long noncoding RNAs in BRAF<sup>V600E</sup> mutant CRC as well as higher angiogenic and lymphangiogenic activity compared to wild-type CRC.

We would like to point out the complementary findings to this study from previous work that has alluded to other parts of the immune landscape of the tumor microenvironment of BRAF<sup>V600E</sup> CRC. From this study, Zhi *et al*[1] reported a higher level of M2 macrophages in BRAF<sup>V600E</sup>-mutated patients compared to the wild-type, with no difference in M1 macrophages levels. Yet, the sample number from which these results were obtained was relatively small (BRAF<sup>V600E</sup> mutation: 10; BRAF wild-type: 20), and this translated to high standard deviations in the M2 counts in both samples. In a recent study by Cen *et al*[2], which used a larger sample (mutated patients: 110, wild-type patients: 798) from the Cancer Genomic Atlas and the Gene Expression Omnibus databases, the authors reported a higher immune cell infiltration and lower tumor purity. Specifically, a higher proportion of CD8+ T cells, M1 macrophages as well as neutrophils were found in BRAF<sup>V600E</sup>-mutated CRC patients, whereas no difference was found in M2 macrophage levels. Furthermore, according to the consensus molecular subtypes' classification, which provides the most comprehensive description of CRC heterogeneity at the gene expression level, BRAF<sup>V600E</sup> mutation is associated with consensus molecular subtype 1, which correlates with high immune infiltration and immune-response pathway activity[3].

Interestingly, subtypes of BRAF<sup>V600E</sup> based on expression patterns in CRC have been further identified. There are two subtypes regardless of microsatellite instability, PI3K mutation status, sex and sidedness: BM1 and BM2[4]. Differences between those subtypes exist, including the prognosis (BM1 was found to have a poorer prognosis than BM2) and the immune status. BM1 has an overall stronger immune profile, emphasized by the activation of pathways like IL2/STAT5, tumor necrosis factor- $\alpha$  signaling *via* nuclear factor kappa B, IL6/JAK/STAT3 and allograft rejection[4]. Taking these subtypes into consideration will reveal a deeper understanding of the tumor immune microenvironment in BRAF-mutated CRC patients.

The immune status of the tumor microenvironment is a multilayered complex subject that leads to crucial implications regarding tumor cell immune evasion, therapeutic response or distant invasion tendency. Therefore, we feel that limiting the immune landscape to the levels of tumor-associated macrophages (M1/2) and cancer-associated fibroblasts, as in the study by Zhi *et al*[1], would not reflect the whole story. This is particularly due to the fact that other key immune components, such as CD8+ and CD4+ T cells, neutrophils, myeloid-derived suppressor cells and regulatory T cells, were not investigated. Of note, higher levels of cytotoxic CD8+ T cells could possibly be neutralized in the tumor microenvironment by immune checkpoints, such as programmed death protein and its ligand or cytotoxic T lymphocyte-associated protein 4[5]. In addition, microsatellite status is of paramount importance in this context, since a higher abundance of CD8+ T cells, activated natural killer cells and M1 macrophages, and upregulated immune checkpoints were identified in microsatellite instability compared to microsatellite-stable CRC[6]. Hence, future investigations including a wider array of immune components, taking into consideration significant genomic features (microsatellite instability and tumor mutational burden), will likely shed light on more reflective findings into the tumor immune status.

In conclusion, the authors presented compelling findings that provide a new perspective on BRAF<sup>V600E</sup>-mutated CRC immune microenvironment by discussing a proposed mechanism for inducing an

immunosuppressed state through the release of exosomal long noncoding RNAs. Future studies targeting this topic should take into consideration the entire spectrum of the dynamic immune activity in the tumor microenvironment, covering relevant immune cells, immune checkpoints and molecular aberrations. Such comprehensive studies will provide insight for promising therapeutic opportunities for this subset of CRC patients.

## FOOTNOTES

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