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Perspective

Immunotherapy Related Prognosis in Colorectal Cancer

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DESCRIPTION

Colorectal Cancer (CRC) is one of the most common malignant tumors and the main cause of cancer death. Since FDA approved immunotherapy for CRC treatment in 2017, patients with CRC have low response to immunotherapy, and there is no effective marker to predict the efficacy of immunotherapy.

In 2020, the incidence of CRC ranks fifth worldwide and the mortality is top five in global cancer related death. In China, CRC incidence is higher, and CRC ranks second in all cancers. With the same time, CRC cancer is the fourth cancer-related cause of death. At present, the treatment of CRC includes surgery, chemotherapy, radiotherapy and immunotherapy (Immune Checkpoint Inhibitors (ICI)). ICI is new therapeutic strategies, which targeting immune checkpoint molecules, including Programmed cell Death protein-1 (PD-1), Programmed cell Death Ligand protein-1 (PD-L1) and Cytotoxic T-Lymphocyte-Associated protein.

ICIs was firstly used to improve the survival of metastatic melanoma, and then used to treat non-small cell lung cancer, leading to FDA approved ipilimumab (anti-CTLA4 antibody), pembrolizumab and nivolumab for the treatment of these solid tumors. In 2017, pembrolizumab and nivolumab attained FDA approval for the treatment of metastatic CRC. CRC can be categorized into two discrete groups: CRC with mismatch repair deficient and microsatellite instability-high (dMMR–MSI-H) and mismatch-repair-proficient and microsatellite instability-low or microsatellite stable CRC. The pMMR–MSI-L CRC accounts for the vast majority of CRC, and approximately 15% of all CRC are dMMR-MSI-H. The dMMR-MSI-H CRC exhibit very high overall mutation burden (>12 mutations per 106 DNA bases) and pMMR-MSI-L signature has a lower mutation burden (<8.24 mutations per 106 DNA bases). Now, several reports have indicated that there is an association between the increase of mutation load and the treatment response of anti-CTLA4-antibody or anti-PD1-antibody. Studies have found that neoantigen load is related to mutation load, so neoantigen load is also related to response. In CRC, ICIs only responded to CRC with dMMR-MSI-H, and it has no clinical benefit on pMMR-MSI-L or MSS CRC. Only a subset of CRC patients benefits from immunotherapy, the precise biomarkers to predict immunotherapy efficacy are needed. Therefore, it is essential to confirm biomarkers and screen the dominant populations of ICIs efficacy.

An extensive immunogenomic analysis was performed to explore the relationship between immune score, prognostic significance, microsatellite status, cancer genotype and potential immune escape mechanism. The IRPS is correlated to important immunophenotypic factors such as neoantigen load and mutation load. Further analysis demonstrated that patients with high IRPS showed therapeutic benefits from immunotherapy.

Here, we make great efforts to establish an immune signature of CRC to analyze the relationship between CRC immune activity, tumor microenvironment and cancer genotype. Based on these prognosis-related immune signature, the immune related prognosis score of CRC was developed, which was found to be related to the overall survival and immunophenotypic factors of patients with CRC. Moreover, we found that the IRPS can predict the patient's response to immune checkpoint blockade.

Our aim is to find a marker that can predict the response of immunotherapy, which can be used to direct the immunotherapy of patients with CRC. Based on these, we can conclude that the IRPS may be an available tool for overall survival prediction and predict immunotherapy of patients with CRC.

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