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Mini Review

Advances in the Study of B-Cell Receptors: From Tumor Characteristics to Clinical Applications

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ABSTRACT

Hepatocellular Carcinoma (HCC) is a global malignant tumor and its complex tumor microenvironment and immune escape mechanism pose great challenges for treatment. In recent years, B-Cell Receptor (BCR) has become a focus of research because of its central role in adaptive immunity. We not only summarize the specific changes of BCR in HCC but also demonstrate that BCR can be considered as a potential biomarker for tumor diagnosis and prognosis prediction. In the future, through the integration of multi-omics data and the mining of the synergistic effect of BCR and T-Cell Receptor (TCR), it is expected to reveal the panorama of the HCC immune microenvironment and promote the clinical transformation of BCR in HCC diagnosis and treatment.

Keywords: Hepatocellular carcinoma; B cell receptor; Clonotype; Complementary determining regions; Chronic lymphocytic leukemia

INTRODUCTION

Hepatocellular Carcinoma (HCC) is one of the most common primary hepatocellular carcinomas worldwide and its morbidity and mortality rates continue to rise in many countries, with its complex tumor microenvironment and high heterogeneity seriously threatening the overall prognosis of patients [1]. B cells, as important immune effector cells, not only participate in the recognition of tumor antigens and immune response but also may mediate specific tumor progression mechanisms through their receptor B-Cell Receptor (BCR) [2]. With the application of single-cell sequencing and high-throughput BCR sequencing technologies, researchers have been able to reveal the composition of B cell subpopulations and the diversity and clonal expansion of their BCRs more precisely. The diversity of BCRs has been considered an important indicator for assessing the adaptability of the immune system and the immune characteristics associated with tumors. Therefore, exploring the mechanism of BCRs in HCC not only contributes to a deeper understanding of the tumor immune microenvironment but also provides potential directions for the development of new biomarkers and immunotherapeutic strategies. This article will review the research progress of BCR in hepatocellular carcinoma, including the diversity of BCR and the characteristics of clonal expansion, as well as the potential of BCR as a biomarker and therapeutic target, in order to provide reference for future research and clinical application.

LITERATURE REVIEW

Composition and biological functions of BCR

BCR is a specific immunoglobulin molecule on the surface of B cells that recognizes and binds antigens to activate B cells and trigger an adaptive immune response. The main functions of BCR include direct recognition of antigens, mediating antibody-dependent immune responses and regulating the immune microenvironment. By binding to antigens, BCR can promote the activation, differentiation and antibody secretion of B cells and participate in humoral immunity and the formation of specific immune memory [3]. BCR consists of two heavy chains (IgH) and two light chains (IgL or IgK) connected by disulfide bonds, each containing a Constant (C) and Variable (V) region. The variable region contains three Complementary-Determining Regions (CDR), namely *CDR1*, *CDR2* and *CDR3*, which are key regions for BCR to bind to antigens. *CDR1* and *CDR2* are determined by the type of gene segment and play a major role in germline diversity. *CDR3*, formed by Variable (V), Diversity (D), and Joining (V(D)J) recombination and non-template insertion of the junction region, shows higher diversity and is the most important region of antigen-binding sites [4].

The diversity of BCRs is the basis for the recognition of multiple antigens by B cells and is produced primarily by two mechanisms. One is the V(D)J gene recombination, that is the V, D and J

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fragments of the heavy chain and the V and J fragments of the light chain are randomly recombined during development, resulting in a large number of receptor variants [5]. The other is Somatic Hyper Mutation (SHM), in which a gene fragment in a variable region undergoes a high-frequency mutation under antigen stimulation, further increasing the affinity of BCR [6]. BCR diversity enables B cells to recognize and respond to various tumor antigens. In tumor immunity, the diversity of BCRs is essential for finding and responding to tumor-associated antigens, revealing mechanisms of immune escape and suppression. The repertoire of BCR reflects the immune state of B cells in a specific environment and its dynamic change is closely related to immune response. When stimulated by antigen, specific BCR clones expand to form the subject of antibody response, which is called clonal expansion. In contrast, after the immune response ends, most B cells die, leaving only a few memory B cells in a process known as clonal contraction. These changes provide a basis for exploring the role of BCR in tumor immunity and may also be a potential target for diagnosis and treatment.

Characteristic changes of BCR in HCC

BCRs play a key role in the immune system, recognizing antigens, mediating the activation and differentiation of B cells and participating in the initiation of humoral immune responses. Through V(D)J recombination and Somatic Hyper Mutation (SHM), BCRs are highly diverse, allowing B cells to recognize multiple antigens and develop highly specific responses to pathogens and tumor antigens. In the tumor environment, BCR not only participates in the recognition of tumor antigens but also reflects the immune system's response to tumors through clonal expansion and dynamic changes. Based on previous studies, we found that the BCR of HCC presents some different characteristics. First of all, in the comparative study of patients with cirrhosis and hepatocellular carcinoma, we found that the BCR variation in HCC patients was significantly reduced. Specifically, the quantity of V(D)J recombination decreased, the clonality index increased, and the Shannon index decreased in HCC patients, and the same situation was also observed in non-small cell lung cancer and acute myeloid leukemia [7,8]. The increased immune selection pressure in the tumor microenvironment leads to clonal-specific amplification of B cells that can effectively recognize tumor antigens while other ineffective or inefficient clones are gradually eliminated [9]. The reduction of BCR variation also limits the ability of B cells to respond to neoantigens, making the tumor microenvironment tend to be immunosuppressive, which has a negative impact on patient prognosis. The other significant change in the BCR clonal profile of HCC patients is specific clonal amplification, which reflects the selective activation and expansion of B cells in the tumor microenvironment. Tumor antigens may lead to a large expansion of a small number of B cell clones with specific BCRs, a process that may have a dual role in the immune surveillance of tumors. On the one hand, clonal amplification can enhance the recognition of specific antigens on the other hand, monoclonal expansion may further reduce the overall diversity of BCR and weaken the overall immune response, thus aiding tumor immune escape. In summary, BCR is not only the core molecule of antigen recognition in the adaptive immune system, but its dynamic changes in the tumor microenvironment reveal the complex response mechanism of the immune system to tumors, providing new ideas and potential targets for tumor diagnosis and treatment.

The potential of BCR as a biomarker in tumor

As a core molecule in the immune system, BCR changes in the tumor microenvironment have become potential diagnostic and prognostic indicators. BCR diversity reflects B cell immune response induced by tumor-associated antigens. Studies have found that BCR diversity is positively associated with improved Skin Cutaneous Melanoma (SKCM) survival and BCR diversity has a potential role in influencing the ability to produce cancer-related antibodies within tumors and when combined with other known parameters, BCR diversity can be a valuable response predictor [10]. The *CDR3* region has also attracted much attention due to its high diversity and direct involvement in antigen binding. In tumor immunity studies, specific sequence patterns of *CDR3* can be used as markers to distinguish tumor patients from healthy controls or different disease states. In our previous study, we used the sequence of *CDR3* as input and random forest algorithm to successfully construct a classifier to identify cirrhosis and hepatocellular carcinoma. The model could make a clear distinction between HCC and Laparoscopic Cholecystectomy (LC) patients (AUC=0.5744-0.887) and the distribution of Receiver Operating Characteristic (ROC) curve was relatively smooth.

The potential of BCR in treatment is also gradually emerging. At present, tumor-specific antigens can be used to activate B cells and induce them to differentiate into antibody-secreting cells, so as to achieve a specific attack on tumors through adaptive immune regulation. This method can enhance the therapeutic effect by designing a personalized BCR vaccine for specific BCR clones or tumor-associated antigens [11]. At the same time, Markl et al., used new light-chain epitopes of BCR defined by feature point mutations to selectively target low-risk subsets of Chronic Lymphocytic Leukemia (CLL) *via* Chimeric Antigen Receptor (CAR) T-cells, also highlighting the important role of BCR in immunotherapy [12]. Targeting the signaling mechanism of BCR, the development of small-molecule or antibody drugs to interfere with its activity is another important direction. For example, Bruton's Tyrosine Kinase (BTK) is a key molecule in BCR signaling and BTK inhibitors have been used to treat a variety of B-cell malignancies [13]. Finally, in-depth research on BCR-related pathways, such as protein-related signaling pathways such as PI3K, will also help us find more potential therapeutic targets [14].

Current challenges and future directions

The function of B cells in tumors shows a dual role, on the one hand, playing a protective role through anti-tumor antibodies and cytotoxic reactions and on the other hand, promoting tumor progression by secreting pro-inflammatory cytokines or supporting immune escape [15]. How to distinguish these two types of reactions using molecular characteristics and functional information is still a major difficulty. At the same time, the key of BCR research is the accurate analysis of high-throughput sequencing data, especially the data integration at the single-cell level. The combination of Single-Cell Ribo Nucleic Acid Sequencing (scRNA-seq) and BCR repertoire sequencing can provide a more refined immune profile, but there are still major challenges in data analysis. In addition, different bioinformatics tools and algorithms process data in significantly different ways, which may lead to inconsistent interpretation of results, limiting the breadth of application of BCR research in cancer.

By integrating multiple omics data, such as scRNA-seq, BCR

repertoire sequencing and spatial omics, we can fully characterize the immune microenvironment of HCC. In particular, spatial omics can retain tissue microenvironment information, which, combined with BCR sequencing, can better locate and analyze the function and dynamic changes of B cells in tumors. In addition, multi-omics data mining the relationship between BCR clonal expansion and diversity and tumor-specific antigens can help to discover new diagnostic and therapeutic targets. In the immune regulation of HCC, the synergistic effect of BCR and TCR may be the key mechanism of anti-tumor immunity. Combining BCR and TCR sequencing data to explore their dynamic interaction and functional linkage is helpful to reveal the complex mechanism of HCC immune response. Further research in these directions may provide a theoretical basis for combined immunotherapy to achieve more effective tumor control.

CONCLUSION

BCR in hepatocellular carcinoma has revealed its multiple potential in tumorigenesis, progression and treatment. As an important component of adaptive immunity, the characteristic changes of BCR represent the immune changes during the development of HCC. The existing tumor characterization and treatment methods based on BCR characteristics also emphasize the research value of BCR. In the future, the in-depth analysis of multi-omics data will further expand the application prospect of BCR in tumor prognosis and treatment and promote its clinical transformation in accurate diagnosis, prognosis monitoring and therapeutic intervention.

DECLARATION OF CONFLICTING INTERESTS

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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