Single-Cell Profiling Explore the Immunologic Mechanisms of Tumor Relapse in Hepatocellular Carcinoma

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Despite the worldwide decrease in liver cancer incidence and mortality over the past decade, it is still the fourth leading cause of cancer-related death. The burden of liver cancer is still serious, especially in China. In 2018, more than half of the liver cancer cases and deaths occurred in China. Hepatocellular carcinoma (HCC) is the most common subtype of liver cancer, accounting for 75% of all liver cancer cases and deaths occurred in China. The high incidence of early recurrence is the main reason for the poor clinical outcomes of HCC. Ignoring the differences between recurrent and primary tumors, recurrent HCCs are often treated based on the pathological characteristics and molecular classification of the primary HCCs. Although previous studies have reported that similar genomic alterations occurred in both primary and early-relapse HCCs, whether primary and early-relapse HCCs have differences in immune contexture is still unknown. The present study dissected and compared the immune contexture at the single-cell resolution level. They found that early-relapse HCC had a distinctive immune contexture that is different from primary HCC. Compared with primary HCC, the density of regulatory T-cells (Tregs) was decreased and those of dendritic cells (DCs) and infiltrated CD8+ T-cells were increased in early-relapse HCC. Additionally, CD8+ T-cells in primary HCC displayed a classical exhausted state, but those in early-relapse HCC overexpressed CD161 and resided in an innate-like phenotype with low clonal expansion and cytotoxic state. These alterations were associated with a worse prognosis in HCC. The authors further explored the potential mechanisms of immune escape in early-relapse HCC. They found that tumor cells in early-relapse HCC could evade the host immune system’s detection and destruction through suppressing DC-mediated antigen presentation and recruiting CD161^high CD8^+ T-cells.

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The following observations of this study reveal why CD161high indicates that these T-cells cannot prevent the spread of HCC. These findings were made in primary HCC. These observations indicate that CD161high CD8+ T-cells manifest as a decrease in the production of granzyme B and (2) T-cell receptor analysis indicated that CD161high CD8+ T-cells in early-relapse HCC reduced clonal expansion and shared most of T-cell receptor clone types with CD8+ T-cells in primary HCC. These findings indicated that CD161high CD8+ T-cells had the ability to target the clonal neoantigens in primary HCCs, but they could not be effectively activated in early-relapse HCCs.

DCs are critical antigen presenting cells. They play a key role in the regulation of the balance between CD8+ T-cell immunity and tolerance to neoantigens. In the present study, enhanced effector functions of CD8+ T-cells were not associated with the increased DC infiltration in early-relapse HCC and suggested that the antigen presentation functions of DCs were impaired in early-relapse HCCs. As we know, CD28 plays a central role in the regulation of T-cell activation and inhibition. Previous study found that programmed death-ligand 1 (PD-L1) has a stronger affinity for CD80 when compared with CD28.14 As early-relapse HCC exhibited more PD-L1+ tumor cells than primary HCC, CD80 on a DC might preferentially bind to PD-L1 on early-relapse HCC cells rather than CD28 on a resting T-cell. Therefore, PD-L1+ recurrence tumor cells may prevent T-cell activation from killing them via reducing CD80–CD28 interactions. If this speculation is true, it means that tumor immunotherapy plus chemotherapy or targeted therapy may be more effective than immune checkpoint blockade as a single agent for patients with recurrent HCC.

Overall, this study provides a comprehensive single-cell profiling in early-relapse HCC and explored the immunologic mechanisms of tumor relapse for the first time. It highlights the potential significance of targeting immune contexture of HCC, and provides a solid foundation for the development of novel therapeutic strategies for recurrent HCC.

**Author’s Contribution**

The author read and approved the final manuscript.

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**Conflict of Interest**

None declared.

**References**