RBM12 drives PD-L1-mediated immune evasion in hepatocellular carcinoma by increasing JAK1 mRNA translation

Han, H., Shi, Q.,et al. (2024). *Oncogene*, 43(41), 3062–3077.

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Date/Time: 2025/06/19, 16:20-17:10
Location: Room 601, Med College Building

Background: Hepatocellular carcinoma (HCC) stands as one of the most common and deadly forms of liver cancer worldwide, with particularly high incidence rates in Asia. Despite advances in treatment options like surgery, radiotherapy, and target therapy, the prognosis for many patients remains poor due to late diagnosis and the tumor's immune evasive capabilities. Immune evasion, primarily through immune checkpoint pathways such as PD-1/PD-L1, allows tumor cells to escape immune surveillance, making immune checkpoint blockade therapies a promising yet limited approach owing to variable patient responses. Recent studies have increasingly focused on the role of RNA-binding proteins (RBPs) in cancer development, but their specific functions in immune regulation and tumor immune escape are not fully understood. This research investigates the role and molecular mechanism of RBM12, a newly identified RBP found to be significantly overexpressed in HCC tissues, in regulation of PD-L1 and immune evasion in HCC .

Objective: This study aims to investigate the role of RBM12 in the immune evasion of HCC and to determine how RBM12 influences PD-L1 expression and tumor immune escape.

Results: The researchers discovered that RBM12 directly interacted with JAK1 mRNA and enhanced the protein level of JAK1 without affecting its mRNA levels. This interaction recruits eIF4A2, a critical translation initiation factor, forming a complex that enhances the loading of ribosomes onto JAK1 mRNA, thereby increasing its translation efficiency. The upregulation of JAK1 protein activates the JAK1/STAT1 signaling pathway. Activation of this pathway leads to increased transcription of PD-L1, a key immune checkpoint molecule that inhibits T cell activity in the tumor microenvironment. Using gene knockout and overexpression strategies both in vitro and in vivo, the authors confirmed that RBM12 significantly promoted PD-L1 expression via enhanced JAK1 translation. Knockout of RBM12 resulted in decreased JAK1 and PD-L1 levels, enhanced T cell activity, and suppressed tumor growth. Conversely, overexpression of RBM12 leads to increased JAK1 and PD-L1 expression, immune escape, and increased tumorigenesis. Studies using in vivo murine HCC models demonstrated that targeted inhibition of RBM12 or JAK1 markedly improved the response to anti-PD-1 therapy, providing compelling evidence that RBM12 is a critical regulator of immune suppression in HCC. Furthermore, analysis of clinical tissue samples of HCC patients showed a positive correlation between RBM12 expression and JAK1/PD-L1 levels.

Conclusion: This study uncovers a novel mechanism by which RBM12 facilitates PD-L1-mediated immune evasion of HCC through the upregulation of the JAK1/STAT1 pathway. Targeting RBM12 or its related pathway could improve immune checkpoint therapies and offer new hope for patients with advanced HCC.