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Regulation of Cancer Immune Escape: The Roles of miRNAs in Immune Checkpoint Proteins

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Abstract：

Immune checkpoint proteins (ICPs) are regulators of immune system. The ICP dysregulation silences the host immune response to cancer-specific antigens, contributing to the occurrence and progress of various cancers. MiRNAs are regulatory molecules and function in mRNA silencing and post-transcriptional regulation of gene expression. MiRNAs modulate the immunity via ICPs have received increasing attention. Many studies have shown that the expressions of ICPs are directly or indirectly repressed by miRNAs in multiple types of cancers. MiRNAs are also subject to regulation by ICPs. In this review, recent studies of the relationship between miRNAs and ICPs (including the PD-1, PD-L1, CTLA-4, ICOS, B7-1, B7-2, B7-H2, B7-H3, CD27, CD70, CD40，and CD40L) in cancer immune escape are comprehensively discussed, which provide critical detailed mechanistic insights into the functions of the miRNA-ICP axes and their effects on immune escape, and be beneficial for the potential applications of immune checkpoint therapy and miRNA-based guidance for personalized medicine as well as for predicting the prognosis.

Keywords: immune checkpoint proteins (ICPs), miRNAs, cancer immune escape

Abbreviations: Antigen-MHC, antigen-major histocompatibility complex; ICPs, immune checkpoint proteins; 3'UTR, 3' untranslated region; PD-1, programmed cell death protein; Tregs, regulatory T cells; HCC, hepatocellular carcinoma; IFN-γ, interferon-γ; IL, interleukin; TNF，tumor necrosis factor；TNFR, cancer necrosis factor receptor; TNF-α, tumor necrosis factor α; APCs, antigen presenting cells; DCs, dendritic cells; NSCLC, non-small-cell lung cancer; MLA, mesenchymal lung adenocarcinomas; CKS1B, CDC28 Protein Kinase Regulatory Subunit 1B; MPM, malignant pleural mesothelioma; TILs, tumor-infiltrating lymphocytes; AML, acute myeloid leukemia; TCR, T cell receptor; HCL, hairy cell leukemia; CLL, chronic lymphocytic leukemia; LNs, lymph nodes; TCKO, T cell-special knockout; ICOS, inducible co-stimulatory molecule; pDCs, plasmacytoid dendritic cells; DCs, dendritic cells; SNP, single nucleotide polymorphism; Tfh, T follicular helper; GC, germinal centre; AGO2, Argonaute 2; AIHA, autoimmune hemolytic anemia; BMDMs, bone marrow–derived macrophages; TLR, Toll-like receptor; CNS, central nervous system; MDSCs, myeloid-derived suppressor cells; BTLA, B and T lymphocyte attenuator; TRAF, TNF receptor associated factor; DNMT1, DNA methyltransferase 1; SP1, transcriptional factor specificity protein 1; SLE, systemic lupus erythematosu; PBMC, Peripheral Blood Mononuclear Cells; CIK, cytokine induced killer; IFNGR, IFN-γ receptor; STAT1, signal transducer and activator of transcription 1; JAK, janus kinase; IRF-1, interferon regulatory factor 1.

1. Introduction

Antigen-major histocompatibility complexes (Antigen-MHC) on antigen presenting cells (APCs) stimulate the proliferation of T cells and the differentiation of effector T cells in secondary lymphoid organs. However, this type of stimulus does not lead to the full activation of the T cells [1]. In the absence of immune checkpoint proteins (ICPs), Antigen-MHC alone results in T-cell anergy. ICPs are indispensable for the full activation of T cells [2-4]. Aberrant expression levels of ICPs are associated with the emergence of T cell exhaustion in many cancers [5]. Escape from the immune system is one of the hallmarks of cancer. Cancer cells modulate the expression