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Comprehensive Analysis of RNA m5C Regulator ALYREF as a Suppressive Factor of Anti-tumor Immune and a Potential Tumor Prognostic Marker in Pan-Cancer

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Abstract : Objective: The RNA methylation recognition protein Aly/REF export factor (ALYREF) is considered one type of "reader" protein acting as a recognition protein of m5C, has been reported involved in several biological progresses including cancer initiation and progression. 5-methylcytosine (m5C) is a conserved and prevalent RNA modification in all species, as accumulating evidence suggests its role in the promotion of tumorigenesis. It has been claimed that ALYREF mediates nuclear export of mRNA with m5C modification and regulates biological effects of cancer cells. However, the systematical regulatory pathways of ALYREF in cancer tissues have not been clarified, yet. Methods: The expression level of ALYREF in pan-cancer and their normal tissues was compared through the data acquired from The Cancer Genome Atlas (TCGA). The University of Alabama at Birmingham Cancer data analysis Portal UALCAN was used to analyze the relationship between ALYREF and clinical pathological features. The relationship between the expression level of ALYREF and prognosis of pan-cancer, and the correlation genes of ALYREF were figured out by using Gene Expression Correlation Analysis database GEPIA. Immune related genes were obtained from TISIDB (an integrated repository portal for tumor-immune system interactions). Immune-related research was conducted by using Estimation of STromal and Immune cells in MAlignant Tumor tissues using Expression data (ESTIMATE) and TIMER. Results: Based on the data acquired from TCGA, ALYREF has an obviously higher-level expression in various types of cancers compared with relevant normal tissues excluding thyroid carcinoma and kidney chromophobe. The immunohistochemical images on The Human Protein Atlas showed that ALYREF can be detected in cytoplasm, membrane, but mainly located in nuclear. In addition, a higher expression level of ALYREF in tumor tissue generates a poor prognosis in majority of cancers. According to the above results, cancers with a higher expression level of ALYREF compared with normal tissues and a significant correlation between ALYREF and prognosis were selected for further analysis. By using TISIDB, we found that portion of ALYREF co-expression genes (such as BIRC5, H2AFZ, CCDC137, TK1, and PPM1G) with high Pearson correlation coefficient (PCC) were involved in anti-tumor immunity or affect resistance or sensitivity to T cell-mediated killing. Furthermore, based on the results acquired from GEPIA, there was significant correlation between ALYREF and PD-L1. It was exposed that there is a negative correlation between the expression level of ALYREF and ESTIMATE score. Conclusion: The present study indicated that ALYREF plays a vital and universal role in cancer initiation and progression of pan-cancer through regulating mitotic progression, DNA synthesis and metabolic process, and RNA processing. The correlation between ALYREF and PD-L1 implied ALYREF may affect the therapeutic effect of immunotherapy of tumor. More evidence revealed that ALYREF may play an important role in tumor immunomodulation. The correlation between ALYREF and immune cell infiltration level indicated that ALYREF can be a potential therapeutic target. Exploring the regulatory mechanism of ALYREF in tumor tissues may expose the reason for poor efficacy of immunotherapy and offer more directions of tumor treatment.

Keywords : ALYREF, pan-cancer, immunotherapy, PD-L1
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