HUMAN RIBONUCLEASES ACT AS POTENTIAL PLASMA BIOMARKERS FOR TARGETED THERAPY AND IMMUNOTHERAPY IN HEPATOCELLULAR CARCINOMA

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Background Ribonucleases, known as RNases, are secreted in the circulatory system that are recognized as part of the host defense system against pathogens. Although RNases are involved in multiple physiologically and pathologically-relevant cell events, including cancer cell growth, stem cell self-renewal and regenerative capabilities, the regulation and function of RNases in cancer therapy remained unclear. Herein, we examined whether RNases could serve as plasma biomarkers to stratify hepatocellular carcinoma (HCC) patients for combination of targeted therapy and immunotherapy.

Methods Two independent HCC patient cohorts were analyzed to evaluate the pathological relevance of RNases. The association between RNases and receptor tyrosine kinases were validated by immunoprecipitation, duolink and immunofluorescence assays. Tumor specimens from HCC patients, who were categorized according to clinical response to nivolumab, were subjected for whole-transcriptome sequencing to identify critical biomarker for combination therapy. The therapeutic efficacy of targeted therapy and immunotherapy was evaluated in HCC orthotopic models.

Results We discovered that RNase7, belongs to RNases super-family proteins, acts as ROS1 ligand and triggers oncogenic transformation independent of its catalytic activities via activation of ROS1 signaling. In addition, clinical data analysis revealed that ROS1 and RNase7 co-expression occurs in approximately 30% of HCC patients and is highly correlated with poorer survival. Moreover, high plasma levels of RNase7 are positively correlated with ROS1 phosphorylation in approximately 45% of tumor tissues from HCC patients. Treatment with crizotinib, which was approved by the FDA for NSCLC patients with ROS1 rearrangement, induces significant anti-tumor effect in mouse models of HCC harboring activation of RNase7/WT ROS1 axis. We also found that RNases family proteins are upregulated in non-responders to nivolumab treatment of HCC patients, and enhances anti-PD1 resistance through regulating macrophage polarization. Blocking RNase-induced pathway activation dramatically enhanced immunotherapy efficacy in HCC orthotopic model.

Conclusions Our findings identified the oncogenic role for human RNase7 in HCC suggesting that RNase7 exhibits a potential to serve as a plasma biomarker to stratify HCC patients for anti-ROS1 targeted therapy. Furthermore, inhibiting RNase function leads to substantial changes to the tumor immune profile in patients with HCC, which may convert immunologically "cold" tumor into "hot" tumor and be effectively combined with immunotherapeutic agents. Clinical research and more patient tissue samples are under evaluation to validate these findings.

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