Linking a Trio of Molecular Features in Clear-Cell Renal Cell Carcinoma

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Clear-cell renal cell carcinoma exhibits unique molecular features, some of which are associated with the response to immunotherapy. However, the interactions between different genomic entities remains incompletely understood. In this issue, Zhou and colleagues show that *PBRM1* inactivation is associated with increased expression of specific human endogenous retroviruses and identify *HIF1/2A* transcriptional activity as an important mediator of this interaction, helping uncover the interplay between some of the key molecular traits of this disease.

See related article by Zhou et al., p. 285 (3).

With the recent advent of immune checkpoint inhibitors (ICI), the treatment of patients with metastatic clear-cell renal cell carcinoma (ccRCC) has substantially evolved, resulting in improved survival. Despite this progress, many patients still experience poor outcomes to immunotherapeutic combinations. To this end, the elucidation of biomarkers of response to current systemic regimens remains crucial. Recently, *PBRM1* loss-of-function (LOF) mutations were found to be associated with response to single-agent ICI therapy administered after disease progression during treatment with a VEGF tyrosine kinase inhibitor (TKI; ref. 1). On the other hand, expression of specific classes of human endogenous retroviruses (hERV) has been linked to improved outcomes in metastatic RCC, notably in patients treated with immunotherapy (2). However, the relationship between these potential biological findings and other RCC-specific features, such as aberrant expression of the hypoxia-inducible factor (*HIF*) gene, has not been thoroughly investigated. In this issue, Zhou and colleagues explore the interplay between the different aforementioned molecular entities (3), furthering understanding of the biology of ccRCC.

First, the authors analyze two datasets of primary RCC tumors with available genomic data (The Cancer Genome Atlas KIRC and IMmotion150 cohorts) and show that *PBRM1* LOF mutations are associated with a higher expression of hERVs, even when accounting for tumor purity as a potential confounder. Notably, this association appears to be specific to ccRCC, as it is not observed in five other tumor types with a high *PBRM1* mutation rate. Further looking into individual hERV classes, the authors show that the HERVERI superfamily is substantially enriched among the retroviruses upregulated in *PBRM1*-mutant RCC tumors. These findings are functionally validated using dedicated RCC cell lines (UMRC2 and A704 cells), where *PBRM1* silencing led to an increase in the expression of multiple hERVs, particularly of the HERVERI superfamily.

Inactivation of the von Hippel-Lindau gene, a defining genomic alteration of ccRCC, results in the accumulation of HIF, leading to the transcriptional upregulation of protumorigenic hypoxia-responsive genes (4). Previous studies have linked *PBRM1* inactivation to an increased *HIF* transcriptional signature, and identified HERV-E, a member of the HERVERI class selectively expressed in kidney cancer, to be regulated by *HIF2A*. In the current study, the authors show that knockdown of either *HIF1A* or *HIF2A* in *PBRM1*-deficient cell lines leads to downregulation of a large proportion of hERVs that initially displayed an increased expression upon *PBRM1* silencing. Some of the originally upregulated hERVs did not appear to be influenced by *HIF1A* or *HIF2A* activation status, suggesting also an independent regulation process among a smaller set of retroviruses.

From a clinical perspective, as both *PBRM1* LOF mutations and specific hERVs have been postulated to represent biomarkers of response to ICIs in RCC in specific therapeutic contexts (e.g., after exposure to VEGF TKIs; refs. 1, 2), the relationship of these findings by Zhou and colleagues with outcomes that make a difference in the clinic remains to be further elucidated. This aligns with the concept of defining ICI response phenotypes in ccRCC, described by our group recently, whereby integrating different tumor, immune, and stromal features, as opposed to considering a single genomic event, might help to better identify responders to therapy (5).

Authors' Disclosures

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