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# Current perspective on the impact of endogenous retroviruses in clear cell renal cell carcinoma

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**ABSTRACT**

**Human endogenous retroviruses (hERVs) have emerged as a mechanism for tumor development and progression in clear cell renal cell carcinoma (ccRCC). Increased expression of various hERVs has been reported in ccRCC with associated activation of anti-tumor immune responses. Retrospective analysis of hERV expression in human ccRCC tumor tissue suggests hERV expression may be associated with improved response to immune checkpoint inhibitors. However, the use of expression to predict response is limited by our ability to annotate and detect hERV expression. This review discusses the biology of hERVs, their role in ccRCC, and the possible impact on ccRCC response to immunotherapy.**

**KEYWORDS**

**Renal Cell Carcinoma, Endogenous Retroviruses, Immunotherapy**

## INTRODUCTION

Kidney cancer is the eighth most common cancer among both sexes in the United States and is estimated to cause 14,890 deaths in 2023[1]. Clear cell renal cell carcinoma (ccRCC) is the most common histologic type of kidney cancer, comprising up to 85% of RCC. ccRCC is characterized by the loss or mutation of the von Hippel-Lindau gene, resulting in constitutive activation of hypoxia-inducible factors (HIF) and upregulation of downstream signaling pathways, including vascular endothelial growth factor (VEGF). Other commonly mutated genes in ccRCC include those that encode chromatin-modifying enzymes, such as SETD2, PBRM1, and BAP-1, and PIK3CA. Over the past 20 years, the treatment paradigm for ccRCC has substantially changed with improved understanding of the underlying tumor biology. However, a mainstay in systemic therapies for ccRCC has been immunotherapy with a relative lack of understanding of the biologic drivers of response and resistance in ccRCC.

Historically, ccRCC has been considered responsive to immunotherapy with interferon-alfa and high-dose interleukin-2 as standard treatments[2,3]. More recently, ccRCC has demonstrated significant response to immune checkpoint inhibitors (ICI), but activity is only observed in a subset of tumors. A proposed mechanism of ICI response in other tumors is high tumor mutational burden (TMB) leading to increased tumor-associated antigens. In melanoma, increased TMB is associated with significantly improved long-term benefit[4]. However, ccRCC demonstrates a lower TMB than other cancers that respond to ICI. For example, melanoma typically has 10-400 mutations per megabase[4], while ccRCC demonstrates an average of 1.1 mutations / Mb[5–7]. Since ccRCC has lower TMB, alternative mechanisms of immunogenicity have been evaluated and expression of human endogenous retroviruses (hERVs) have been identified as a possible biomarker of response.

Over the past couple of decades, hERVs have been increasingly recognized as upregulated in human cancers[8–16]. Additionally, hERV products have been shown to elicit antitumor immune response in both renal cell carcinoma and other tumor types[17–22]. Recent studies highlight the significant role that hERVs may play not only in the development and progression of ccRCC, but also the response to immunotherapy[15,23–25]. In this review, we focus on the biology of hERVs, their identified roles in RCC, and how hERVs may impact response to immunotherapy in ccRCC.

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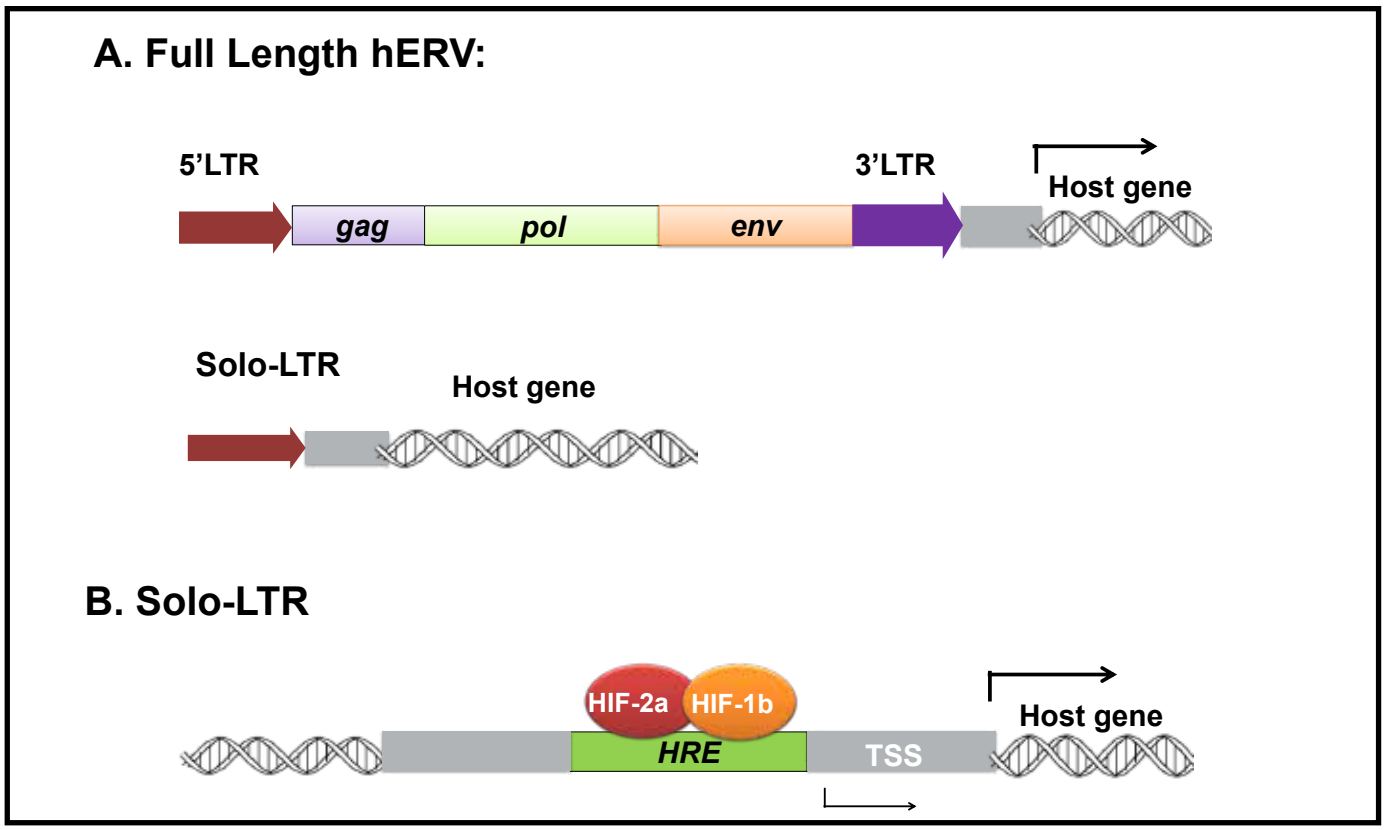


**FIGURE 1 | The structure of hERVs retains gene regulatory elements, such as hypoxia response elements (HREs).** **A.** Full-length hERVs consist of gag, pol, env, and 5′ and 3′ LTRs. Solo-LTRs lose gag, pol, and env, retaining an LTR and the included gene regulatory elements. **B.** Regulatory elements retained in solo-LTRs, such as hypoxia response elements (HRE) or transcriptional start sites (TSS), can be bound by transcription factors, such as hypoxia inducible factor (HIF), to promote expression of both hERVs and regulated genes.

## The biology of endogenous retroviruses

Human endogenous retroviruses (hERVs) are endogenous viral components present in the human genome which originated as retroviruses millions of years ago and were incorporated into the genome of germ line cells. hERVs form the majority of long terminal repeats (LTRs) and comprise about 8% of the human genome26. While hERVs are defective in viral replication and typically lose the ability to encode proteins, they contribute to regulation of the human genome by acting as promoters, enhancers, repressors, poly-A signals, and alternative splice sites for human genes[19]. hERVs are typically silenced in normal somatic tissues19, but hERV expression has been reported as increased in a variety of cancers[8–14], including ccRCC[15,17,18], autoimmune disease, and neurological disorders[27–30].

Over 50 families of hERVs have been identified and are categorized into classes I-III[26]. For example, HERV-E and HERV-H are class I, while HERV-K is a class II hERV[26]. The structure of each individual hERV typically contains gag, pol, and env components, which are flanked on the 5' and 3' ends by two gene regulatory sequences, long terminal repeats (LTR)[26]. While most of the hERVs in the human genome lose coding ability, a few hERVs retain the ability to encode functional proteins, such as HERV-K and HERV-W[31,32]. Loss of hERV coding ability can be due to non-allelic homologous recombination between the 3' and 5' LTRs, resulting in solo-LTRs and loss of the gag, pol, and env components[33,34]. Within the human genome, hERVs typically exist in the solo-LTR form and maintain gene regulatory function through the presence of transcriptional regulatory motifs[34,35] (FIGURE 1). However, some hERVs, such as those in the ERVK family, do preserve a functional gag gene or open-reading frame for the pol and env genes[36].

hERVs may promote tumorigenesis through a variety of mechanisms. First, expression of hERVs can activate tumor-promoting signaling pathways, including the RAS-ERK and Wnt/β-catenin pathways[8,37,38], which promote cell proliferation and transformation. Second, the hERV envelope protein, syncytin-2, has been shown to have immunosuppressive properties[39]. However, hERV expression also promotes the detection of tumors by the immune system. Immunotherapy research in other tumor types has demonstrated that a subset of HERV-K and HERV-H proviruses express immune-stimulating antigens on tumor cells, which can then be recognized and killed by cytotoxic T-cells[20,22].

## Endogenous retroviruses in clear cell renal cell carcinoma

Over the past two decades, hERV expression has been strongly implicated in the development and progression of ccRCC and is associated with clinical outcomes. First, multiple hERVs demonstrate increased expression in ccRCC, including HERV-E[16,18], HHLA2[40], and HERVERI[41]. Interestingly, expression of HERV-E in ccRCC appears to be interrelated to the underlying tumor biology. HERV-E expression levels correlate with HIF-2α levels and HERV-E expression was abrogated by introduction of normal VHL or HIF-2α knock-down[16]. Additionally, HIF-2α can act as a transcriptional factor for HERV-E by binding a HIF response element (HRE) located in the proviral 5' long terminal repeat (LTR)[16]. Cherkasova *et al.*, also demonstrated that this LTR was hypermethylated in normal tissues, preventing hERV expression, and hypomethylated in HERV-E expressing ccRCC tumors[16], allowing for increased expression. In a separate study, Siebenthall *et al* identified HIF-binding to other LTR sites genome-wide which correlated with gene expression changes in RCC, including HIF binding at an HRE in an hERV LTR located upstream of the stem cell transcription factor POU5F1 (OCT4), resulting in increased POU5F1 expression levels[42].

Increased hERV expression is also associated with PBRM1 loss in primary human ccRCC tumors[41]. PBRM1 is the second most frequently mutated gene in ccRCC5 and encodes a member of the PBAF (polybromo BRG1 associated factor) SWI/SNF chromatin remodeling complex[43,44]. This SWI/SNF complex regulates nucleosome positioning and gene expression[43,44]. We utilized the UMRC2 kidney cancer cell line to confirm that *in vitro* silencing of PBRM1, HIF1, and HIF2 resulted in increased expression of hERVs in a HIF1 and HIF2 dependent manner[41]. We also identified a specific family of hERVs, the HERVERI superfamily, that are enriched in PBRM1-regulated hERVs[41]. Therefore, expression of the HERVERI superfamily is dependent upon loss of function mutations in two genes that are highly specific to ccRCC, VHL and PBRM1, and may explain its unique association with this cancer.

Furthermore, the expression of hERVs in ccRCC is immunogenic, activating T-cell responses. First, in a study utilizing TCGA datasets from 18 tumor types, Rooney *et al.* identified that high immune cytolytic activity in ccRCC is associated with elevated expression of the HERV-E loci, ERVE-4[45]. Additionally, Cherkasova *et al.* demonstrated that proteins predicted to encode the HERV-E envelope protein (HLA-A*0201-restricted

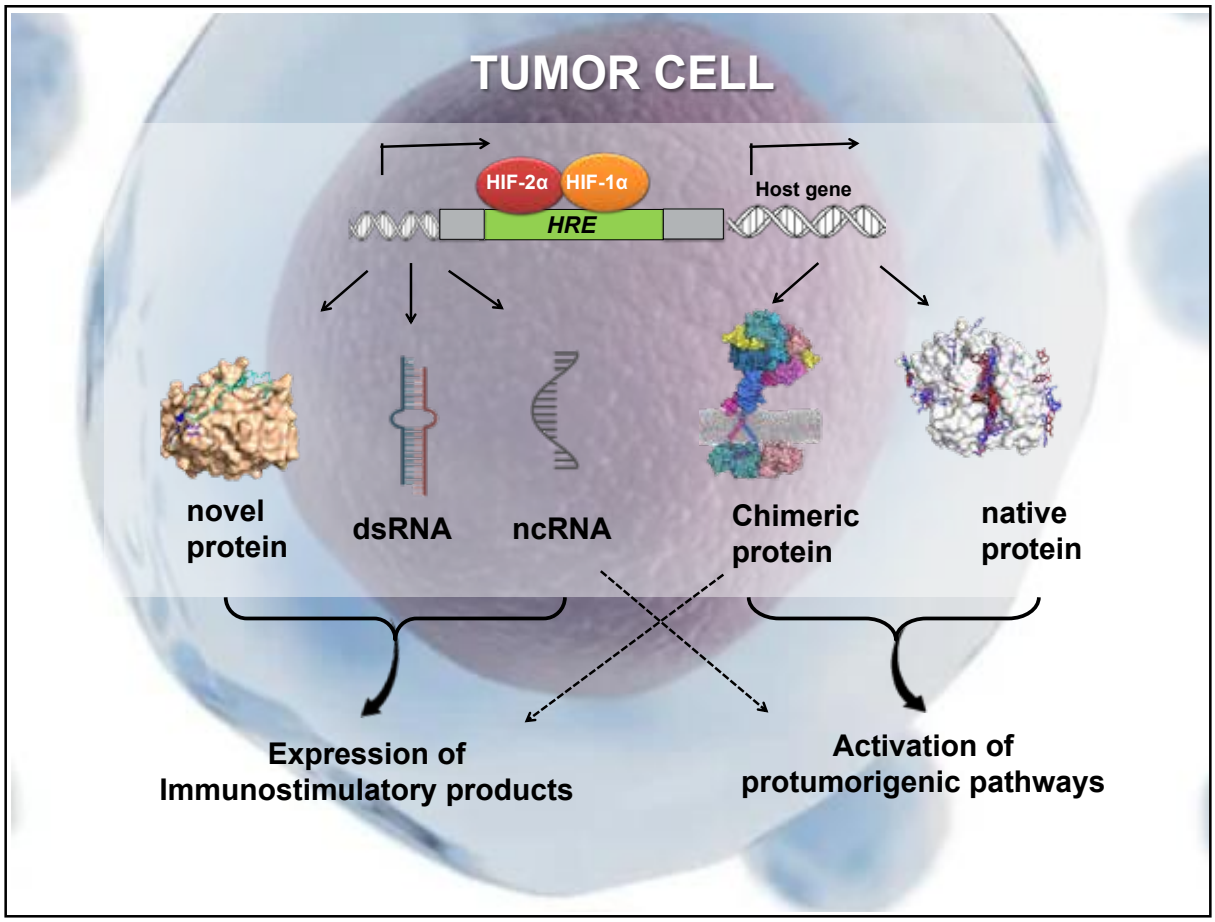


**FIGURE 2: Proposed mechanism of the association between ICI response and hERV expression.** In tumor cells, expression of solo-LTRs is proposed to result in the expression of RNA (including non-coding RNA (ncRNA) or double-stranded RNA (dsRNA)) or provirus-derived proteins which act as tumor-specific antigens which can induce tumor-specific immune cell responses or activation of pro-tumorigenic pathways. In the setting of ICI, we hypothesize that neoantigens promote a more robust immune cell response, allowing for improved response to ICI.

peptides) are expressed in ccRCC tumors and are immunogenic in vitro[17]. Furthermore, in a patient demonstrating regression of renal cell carcinoma after receiving an allogeneic hematopoietic stem cell transplant, a CD8+ T-cell clone recognizing a HERV-E antigen was isolated[18], suggesting tumor-specific T-cell reactivity in response to HERV-E expression. These results indicate that hERV- based antigens could act as targets for possible T-cell derived immunotherapy in ccRCC.

Finally, the expression of hERVs in ccRCC is associated with patient clinical outcomes. Human endogenous retrovirus-H long terminal repeat-associating protein 2 (HHLA2) demonstrates increased expression in ccRCC compared to normal kidney tissue at both RNA and protein levels[40] and HHLA2 expression was associated with poor overall survival[40]. Additionally, in a study utilizing the TCGA (The Cancer Genome Atlas) pan-cancer dataset, mean hERV expression in ccRCC was significantly negatively prognostic for overall survival and, when comparing Kaplan Meier curves for the upper versus lower 50$^{th}$ percentile mean hERV expression, ccRCC was one of only five tumor types that demonstrated significant separation of survival curves[15]. Of these five tumor types, ccRCC demonstrated the most significant association, with higher hERV expression associated with significantly shorter overall survival[15]. Further work in this dataset identified possible hERV signaling through the RIG-I-like pathway and B-cell activation and patients with both higher expression of B-cell receptor-associated signatures and down-regulation of RIG-I-like signatures demonstrated significantly shorter overall survival[15].

## The impact of ERVs on response to immunotherapy in RCC

The introduction of immune checkpoint inhibitors (ICI) for the treatment of ccRCC has significantly improved patient outcomes. However, significant responses are only observed in a subset of patients and much work has focused on identifying predictive biomarkers. Given the immunogenicity of hERV expression discussed above, studies have utilized patient samples from ICI clinical trials to assess the association between hERV expression and tumor response to ICI.

In 24 metastatic ccRCC tumors treated with single-agent PD-1/PD-L1 blockade, ICI responders demonstrated significantly higher expression of ERV3-2 than non-responders[23]. Using the TCGA KIRC dataset, this study also demonstrated that high expression of twenty hERVs that were identified as potentially immunogenic was associated with increased immune infiltration, checkpoint pathway upregulation, and a higher CD8+ T-cell proportion in tumor infiltrating leukocytes compared to low hERV expression[23]. By performing qRT-PCR on tumor samples from CheckMate010, Pignon *et al.* also evaluated the association between 4 hERVs (pan-ERVE4, pan-ERV3.2, hERV4700 GAG, and hERV4700 ENV) and response to nivolumab[24]. Using a cutoff of the 25th percentile, high levels of hERV4700 ENV were associated with significantly longer median progression free survival and higher overall response rates[24]. Similarly, using tumor samples from CheckMate 025, Ficial *et al.* identified that in ccRCC tumors treated with nivolumab, higher hERV-E RNA expression levels were associated with increased durable response rate and longer progression-free survival[25]. Additionally, in the previously mentioned TCGA pan-cancer dataset, a transcriptional signature indicating anti-PD1 responsiveness (IPRES_aPD1_responder) demonstrated positive association with hERV expression in 79.2% of significantly associated hERVs in all tumor types[15]. Within ccRCC specifically, higher expression of hERV 4700 was associated with response to anti-PD1 therapy[15]. When combined, these studies suggest that high hERV expression may identify patients who might respond to ICI. FIGURE 2 illustrates a proposed mechanism for this improved response in the setting of hERV expression.

However, when Braun *et al.*, subsequently pooled data from CheckMate009, CheckMate010, and CheckMate025, they did not identify a robust association between hERV expression and response to immunotherapy. In this study, they first validated RNA-seq-based expression of hERV using qRT-PCR and demonstrated that RNA-sequencing did not reliably quantify ERV3-2 expression. However, they did identify a weak association between ERV2282 and ERV3382 expression with response and overall survival and progression free survival. However, when divided into high and low expression levels, the significant association with PFS and OS did not persist[46].

Additionally, using tissue from the ADAPTeR trial, in which patients with metastatic ccRCC were treated with nivolumab, Au *et al* concluded that ccRCC-specific hERV expression did not directly correlate with response to anti-PD-1 treatment[47]. Specifically, they performed RNA-sequencing on a total of 60 tumor samples from 14 patients and annotated hERVs using a previously built "complete custom repeat region annotation"[48]. Even when accounting for annotation discrepancies between prior analyses, the hERVs previously identified as associated with cytotoxic T-cell presence, ccRCC response to ICI, or providing antigens were not differentially expressed between ICI responders and non-responders or associated with ICI response in this study[47]. However, 10 different hERV annotations were significantly associated with ICI response but demonstrated a mix of restriction to responders versus non-responders, demonstrating a different pattern of hERV association with ICI response than observed in the above studies[47]. Based on

these results and data indicating that hERVs previously reported as upregulated in ccRCC may be expressed on immune cells, Au *et al* suggest that hERV expression in ccRCC may reflect tumor purity and the diverse cellular composition of ccRCC tumors[47].

As described above, PBRM1 loss is associated with increased expression of hERVs in primary ccRCC human tumors and additional work has evaluated the interplay between PBRM1 mutation, hERV expression, and ICI response. First, previous work has evaluated predictors of ICI response in ccRCC and variably identified PBRM1 mutations as a predictive biomarker[46,49–53]. While studies identified an association between PBRM1 loss of function mutations and second-line, single-agent ICI response[46,49,50,53], additional groups evaluating PBRM1 mutations and ICI response in first-line treatment with combination VEGF inhibitor and ICI did not identify an association[51,52]. Additional work by Liu *et al* highlights the role that HIF plays in this response since PBRM1 deficient, HIF axis-intact cells show ICI resistance[54]. This study utilized VHL and PBRM1 wild-type RENCA cells, which are murine-derived RCC cells from a BALB/c background, in which PBRM1 knockout was achieved using CRISPR/Cas9 technology[54]. When introduced into mice subcutaneously, both PBRM1 wild-type and knockout cells established tumors and PBRM1 knockout tumors showed worse survival than control tumors following treatment with PD-1 antibody[54]. Further evaluation of how the concurrent loss of PBRM1 and VHL impact ICI response is needed.

In addition to using hERV expression as a predictive biomarker for ICI response, future directions can also explore alternative approaches to exploiting the biology of hERVs. First, as hERVs are immunogenic, they may have the capacity to serve as vaccine targets. Indeed, in a mouse model with tumors formed from murine renal carcinoma cells (Renca) altered to express the HERV-K Gag proteins, mice vaccinated using a recombinant virus expressing the HERV-K Gag protein demonstrated reduced tumor growth and reduction in pulmonary tumor nodules[55]. Similar results were observed when mice with tumors expressing HERV-K Env proteins were vaccinated against the HERV-K Env protein[56]. Second, it may also be possible to manipulate the expression of hERVs to increase response to immunotherapy. For example, kidney cancer cell lines and primary cells that were treated with a DNA hypomethylating agent, decitabine, demonstrated increased expression of transposable elements, LINE1, and ERVs ERV3-2 and ERV4700, which were associated with immune infiltration and ICI response on bioinformatic analysis[57]. Finally, work investigating the impact of treating HLA-A*11:01 positive patients with metastatic ccRCC with HERV-E TCR transduced CD8+ and CD34+ enriched T-cells is ongoing (NCT03354390) and remains a promising option for exploiting hERV expression to more effectively treat ccRCC.

## CONCLUSIONS

A subset of ccRCC tumors demonstrate increased expression of human endogenous retroviruses, endogenous viral components which have been incorporated into the human genome. ccRCC expression of hERVs seems to be interrelated to its distinct underlying tumor biology, with hERV expression levels related to both the VHL-HIF pathway and PBRM1 loss. Furthermore, the expression of hERVs in ccRCC is immunogenic, resulting in activation of tumor-specific T-cell responses in vitro and *in vivo*, and studies in mouse models highlight the potential for hERVs to act as vaccine targets. While higher hERV expression is associated with worse overall survival in ccRCC, data evaluating the association between hERV expression and response to ICI is conflicting. While single study reports identified encouraging associations with improved patient outcomes, only weak associations were observed when studies were combined, possibly reflecting differences in intratumoral heterogeneity and the tumor microenvironment. As such, additional knowledge of the mechanisms and pathways by which HERVs impact ccRCC tumorigenesis and therapeutic response is needed for optimal therapeutic development and continued improvements in patient outcomes.

## FUTURE DIRECTIONS

Further investigation of the impact of human ERVs on the pathogenesis and progression of ccRCC will allow for improved understanding of the role ERVs play in response to therapies. Additionally, utilizing tissue from clinical trials assessing response to combination immunotherapy or prior to receiving systemic therapy may shed light on the seeming discrepancies in the association of hERV expression and ICI response. Finally, a broader understanding of the biology of hERV in ccRCC is necessary, including 1) characterizing the expression of hERVs in ccRCC tumor cells versus the tumor microenvironment; 2) elucidating the key downstream signaling pathways activated by hERVs and the interplay with VHL loss and chromatin modifying enzymes, and 3) identifying additional tumor-specific antigens. Further knowledge of the key cell types, antigens, and signaling pathways impacted by hERVs will allow further development of synergistic therapies and optimization of first-line treatments for individual patients.


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