> the study reveals the biological and clinical significance of the L-2-HG–L2HGDH axis

reduction of L-2-HG levels (via genetic restoration of L2HGDH) decreased H3K27me3 levels and increased H3K 27me3 target gene expression in RCC cells, suggesting that L-2-HG can influence epigenetic states. Indeed, L-2-HG has previously been shown to inhibit lysine-specific demethylase 6A (KDM6A), which demethylates H3K27 me3 and is frequently mutated in RCC.

In an RCC TCGA data set, low *L2HGDH* expression was associated with poor survival outcomes and high tumour stage and grade, and tumours with loss of heterozygosity at the *L2HGDH* locus had worse survival outcomes than those without such alterations, demonstrating the translational relevance of the findings.

Overall, the study reveals the biological and clinical significance of the L-2-HG–L2HGDH axis in RCC. "We are now looking at therapeutics for L-2-HG-driven renal tumours and at utilizing L-2-HG as a biomarker," concludes author Sunil Sudarshan.

Conor A. Bradley

ORIGINAL ARTICLE Shelar, S. et al. Biochemical and epigenetic insights into L-2-hydroxyglutarate, a potential therapeutic target in renal cancer. *Clin Cancer Res.* https://doi.org/10.1158/1078-0432.CCR-18-1727 (2018)

> *Rarg* expression reduced and miR-96 expression increased in line with prostate cancer development

cancer development. This association was also observed in patient samples.

"Relatively small changes in miR-96 expression have a potentially amplifying effect on the functionality of RARγ, which has considerable influence on AR signalling," explains Campbell. "Patients with tumours with high miR-96 and low RARγ expression had significantly worse outcomes in terms of time to disease recurrence," he continues.

Serum levels of miR-96 could be a useful diagnostic biomarker for prostate cancer and miR-96 has the potential to be a therapeutic target. Targeting retinoid signalling in prostate cancer should be revisited in clinical trials. "The genomic functions of nuclear receptors, such as RARγ, could have been overlooked as a result of the focus on the steroid hormone nuclear receptors," concludes Campbell.

Louise Stone

ORIGINAL ARTICLE Long, M. D. et al. The miR-96 and RARγ signaling axis governs androgen signaling and prostate cancer progression. *Oncogene* https://doi.org/10.1038/s41388-018-0450-6 (2018)

KIDNEY CANCER

Retroviral signature can predict therapy outcome

New data suggest that expression of transcriptionally active human endogenous retroviruses (hERVs) is associated with prognosis in clear cell renal cell carcinoma (ccRCC) and that hERV signatures associated with specific immune mechanisms could predict patient survival.

"Unlike other immunotherapy-sensitive tumours, ccRCC is not characterized by a high mutation burden, despite a high response rate to immunotherapy," explains lead author Ben Vincent. "This led us to the hypothesis that other factors in ccRCC, including hERV expression, could alter the tumour microenvironment and affect response to immunotherapy."

Vincent's team designed a computational workflow (hervQuant) for identifying hERV expression from The Cancer Genome Atlas (TCGA). Different cancers displayed similar hERV expression patterns; however, testicular germ cell tumour and uveal melanoma, which arise from immune-privileged tissues, had less similar profiles, suggesting that the shared hERV expression profiles in other tumour types might have been affected by tumour immune responses.

Multivariable linear regression of hERV expression by cancer type examined the association between hERV expression and immune features, age, and overall survival (OS). Significant hERVs included those associated with immune cells known to have antitumour functions, including effector and central memory T cells and natural killer (NK) cells. Furthermore, a signature of anti-programmed cell death 1 (PD-1) was positively associated with hERV expression, and a signature for anti-PD-1 in nonresponder tumour biopsies was negatively associated with all hERV expression. Cox regression of hERV expression and clinical outcome showed that patients with greater mean hERV expression had worse outcomes in all cancers except bladder cancer. Of all the cancer types included in TCGA, ccRCC contained the greatest number of prognostic hERVs. Thus, the role of hERVs in ccRCC was further examined, focusing on two mechanisms by which hERV expression could influence the tumour immune microenvironment: activation of retinoic acid-inducible gene I (RIG-I)-like pathway signalling and hERV epitope-triggered T cell and B cell activation.

Study of the association between hERV expression and genes in the RIG-I-like receptor signature led to the identification of two biologically distinct hERV groups. Both groups showed positive associations between hERV expression and agonistic genes to the RIG-I-like pathway, but group 2 hERVs were also positively associated with key antagonist genes in the nuclear factor-κB (NF-κB) pathway and negatively associated with NF-κB agonistic genes. Regression analysis of hERV expression in the ccRCC TCGA cohort showed that the majority of group 1 hERVs were associated with longer OS, whereas group 2 hERVS were associated with shorter OS. In addition, presence of B cell receptors was associated with hERV expression, suggesting a hERV-epitope-driven B cell response.

The hERV identified as the most differentially expressed with greatest evidence of translation (hERV 4700) was tested for predictive ability of patient response to anti-PD-1 therapy. The hERV 4700 reverse transcription quantitative PCR signal and hervQuant-derived hERV 4700 expression were both greater in anti-PD-1 responders than nonresponders, indicating that hERV 4700 transcription could be associated with increased responsiveness to immunotherapy.

In their discussion, the authors assert that "hERVs may either directly interact with antitumour immunity through immune activation or provide a biomarker for an active antitumour immune response."

Annette Fenner

ORIGINAL ARTICLE Smith, C. C. et al. Endogenous retroviral signatures predict immunotherapy response in clear cell renal cell carcinoma. *J. Clin. Invest.* https://doi.org/10.1172/JCI121476 (2018)