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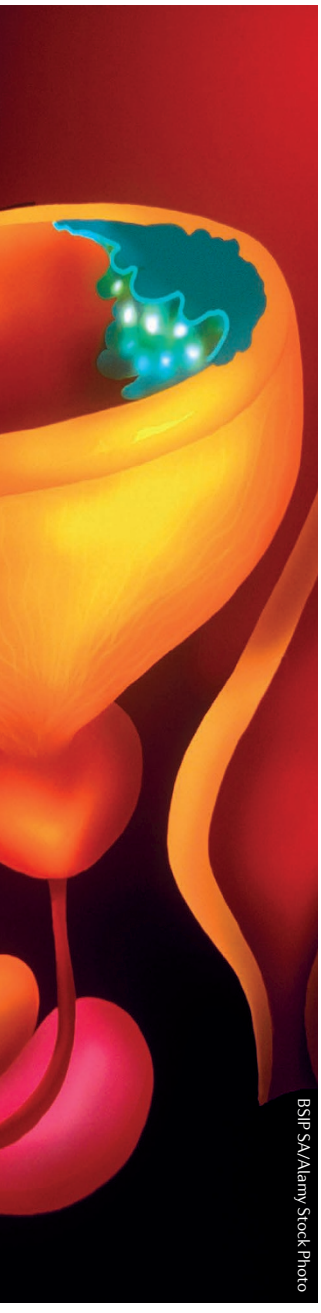
BLADDER CANCER

PPARγ-RXRα alterations promote immune evasion



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The introduction and subsequent FDA approval of antibodies that inhibit immune checkpoints or their endogenous ligand, such as the anti-PD1-antibodies nivolumab and pembrolizumab, or the anti-PD-L1 antibodies atezolizumab, avelumab and durvalumab, has dramatically improved the outcomes of a subset of patients with metastatic urothelial carcinoma. However, despite these improvements, the majority of patients fail to respond to such agents. Now, the findings of a translational study shed light on the complex reasons for this lack of a response in most patients. Lead author Ping Zhu explains "in an unbiased analysis we identified an anticorrelation between peroxisome proliferator-activated receptor γ (PPARγ) activity and immune-cell infiltration into bladder tumours, indicating the importance of PPARγ signalling in immune evasion and responses to immunotherapies".

Researchers originally identified the relevance of genetic aberrations in either PPARγ or retinoic receptor α (RXRα), which form the PPARγ/RXRα heterodimer, to antitumour immunity using bioinformatic analyses. This initial finding was then pursued further using biophysical assays to confirm the effects of these aberrations on signalling, followed by crystallography, which confirmed the presence of an interaction between the two proteins. Animal models and analyses of clinical samples were then used to confirm that such alterations are present *in vivo* and in the clinic.

Aberrations in either *PPARγ* or *RXRα* were detected in almost 40% of muscle-invasive bladder cancer (MIBC) specimens in The Cancer Genome Atlas (TCGA) dataset, with $RXR\alpha^{S427F/Y}$ and *PPARγ* amplifications being the most commonly observed alterations. Both alterations were significantly more abundant among luminal MIBC, with a trend towards mutual exclusivity, suggesting that both alterations have similar roles. Analyses of the crystal structure of $RXR\alpha^{S427F}$ demonstrated that this mutation confers enhanced binding affinity for PPARγ, which enables the formation of heterodimers in a ligand-independent manner. The functional consequences of this interaction were then confirmed as a PPARγ-dependent increase in the expression of several established PPARγ target genes. Building on the observed suppression of immune-related signalling pathways identified in samples from the TCGA cohort, transfection with $RXR\alpha^{S427F}$, $RXR\alpha^{S427Y}$, or *PPARγ* overexpression in T24 cell lines resulted in suppression of IL-6, IL-8 and other inflammation-signalling pathways. In order to further explore this interaction, researchers generated an 'immune signature' consisting of genes associated with activation of the immune system, including inflammation-related genes. Similar to previous findings, high levels of PPARγ expression were correlated with reduced expression of many genes in the immune signature, and a similar association was observed in samples of $RXR\alpha^{S427F/Y}$-mutant MIBC from TCGA, and several other databases. These changes in gene expression were then demonstrated, in samples from an independent cohort, to result in a significant decrease in infiltration by $CD8^+$ T cells.

In order to explore the clinical consequences of aberrant PPARγ/RXRα signalling, a syngeneic MBT2 mouse model of bladder cancer overexpressing either S427F or wild-type forms of RXRα was created. Mice overexpressing $RXR\alpha^{S427F}$ had substantially fewer $CD3^+$ or $CD8^+$ infiltrating T cells, compared with their wild-type counterparts. When exposed to immunotherapy with anti-CTLA4 antibodies, RXRα-wild-type mice had a significant reduction in mean tumour volume at day 7, compared with no significant changes in mice overexpressing the S427F variant.

These findings demonstrate that mutations in the genes encoding PPARγ and RXRα, which together form the PPARγ-RXRα heterodimer confer partial resistance to immune-checkpoint inhibition. First author Manav Korpal highlights "The timing of these findings is critical for several reasons: understanding the molecular mechanism underlying immune evasion and lack of response to immunotherapies in patients with MIBC; the potential to identify biomarkers predicting a response to immune-checkpoint inhibition; and potential therapeutic strategies (combining immunotherapy with a PPARγ inhibitor) that might sensitize patients whose disease is currently deemed resistant to such therapies".

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