

IMMUNE CHECKPOINT BLOCKADE BOOSTS ANTI-TUMOUR B CELL RESPONSES IN LUNG ADENOCARCINOMA

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Background B cells are frequently found in the margins of solid tumours, where they are organized in tertiary lymphoid structures (TLS) that resemble antibody-producing germinal centres. The presence of TLS has been associated with improved patient outcome and response to immunotherapy, though the mechanisms underlying these associations remain unclear. Similarly, the contribution of B cells and TLS to anti-tumour immunity in non-small cell lung cancer (NSCLC) remains largely unexplored.

Methods We evaluated treatment-naive NSCLC cohorts to compare B cell and TLS gene signatures from human lung adenocarcinoma (LUAD) and squamous cell carcinoma (LUSC). Using a novel immunogenic mouse model of LUAD, we carried out lineage tracing, 3D immunofluorescence, and single-cell sequencing to characterise lung germinal centre and antibody responses during tumour progression and immunotherapy treatment.

Results B cell and TLS genes were significantly higher in LUAD compared to LUSC and correlated with improved survival. We therefore investigated the mechanistic basis of B cells in LUAD using a novel immunogenic KRAS-mutant lung cancer mouse model. Using serum transfer experiments, we demonstrated a highly protective role for tumour-binding class-switched antibodies. These germinal centre B cell responses and antibody quantity were increased after immunotherapy treatment or targeted KRAS inhibition. Interestingly, tumour-binding antibodies were demonstrated to be targeting re-expressed endogenous retroviral (ERV) antigens. Using single-cell BCR sequencing of immunotherapy-treated mice, we showed clonal expansion of B cells reactive to ERV antigens. Furthermore, ERVK-7 which encodes an endogenous retrovirus envelope glycoprotein was overexpressed in human LUAD and therefore may act as a relevant tumour antigen. Finally, we showed that combined treatment with CXCL13 and immune checkpoint blockade improved survival, suggesting that boosting local B cell responses can improve immunotherapy outcome.

Conclusions Our work describes a novel role for B cells in lung cancer and establishes that TLS directly contribute to anti-tumour immunity by producing class-switched protective antibodies. We demonstrate that selective boosting of anti-tumour B cells shows therapeutic potential in combination with immune checkpoint blockade.

Ethics Approval All animal experiments were approved by the ethics committee of the Francis Crick Institute and conducted according to local guidelines and UK Home Office regulations under the Animals Scientific Procedures Act 1986 (ASPA).

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