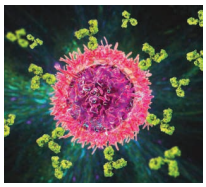
Kidney Cancer

Major Finding: Locally generated plasma cells initiate an antibody-mediated antitumor response in kidney cancer.

Concept: Tertiary lymphoid structures (TLS) serve as intratumoral sites of antitumor plasma cell maturation.

Impact: This study suggests a mechanism that underlies the association between TLSs and patient response.

ANTITUMOR PLASMA CELLS MATURE WITHIN TERTIARY LYMPHOID STRUCTURES



Defined as lymphoid aggregates that develop in nonlymphoid tissues, tertiary lymphoid structures (TLS) can be found within the tumor microenvironment and are associated with improved clinical outcomes in multiple cancer types. Consisting of dendritic, T, and B cells, TLSs can serve as sites of immune activation and also harbor germinal centers, which promote maturation of B cells into antibody-secreting plasma cells (PC). To investigate how B cells and PCs may impact the antitumor response, Meylan and colleagues studied the features of intratumoral TLSs in tumor samples from patients with clear-cell renal cell carcinoma (ccRCC). Spatial transcriptomic analyses of TLS^+ and TLS^- tumor tissue suggested an association of TLS areas with a gene signature corresponding to the B lineage, which includes the maturation stages between immature B cells and terminally differentiated PCs, as well as T-cell and fibroblast gene signatures. Comparison of TLS areas with surrounding tumor tissue enabled creation of a 29-gene TLS imprint signature, including immunoglobulin genes such as *IGHA1* and *IGHG1*, B-cell markers including *MZB1*, and fibroblast markers like *CXCL12*. Supporting the concept of intratumoral *in situ* B-cell maturation toward PCs, spatial B-cell receptor profiling analysis revealed evidence of somatic hypermutation and clonal selection, with colocalization analyses indicating the presence of IgG- and IgA-expressing PCs within TLSs as well as the dissemination into tumors upon a network of $CXCL12^+$ fibroblasts. Antibody-producing PCs densely surrounded tumor cells strongly labeled with IgG, highlighting antibody-dependent cellular cytotoxicity (ADCC) as a potential PC-mediated antitumor response. Accordingly, in samples with abundant IgG tumoral staining and a robust amount of apoptotic tumor cells, $CD68^+$ macrophages, one of the main effectors of ADCC, were correlated with cleaved caspase 3^+ (a marker of apoptosis) tumor cells. Notably, there was also a positive correlation between high tumoral IgG staining and response to immune checkpoint inhibitors in patients with ccRCC. In summary, this study indicates the importance of intratumoral PC maturation in an antibody-mediated antitumor response and supports its association with immunotherapy outcomes. ■

Meylan M, Petitprez F, Becht E, Bougoüin A, Pupier G, Calvez A, et al. Tertiary lymphoid structures generate and propagate anti-tumor antibody-producing plasma cells in renal cell cancer. Immunity 2022; 55:527–41.e5.

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Drug Resistance

Major Finding: Resistance to noncovalent BTK inhibitors is mediated by non-C481 BTK and PLCγ2 mutations.

Concept: These mutations impair drug binding as well as allow effective signaling despite hindering BTK catalytic activity.

Impact: New mechanisms of escape were demonstrated that confer resistance to both noncovalent and covalent BTK inhibitors.

ON-TARGET BTK MUTATIONS PROMOTE RESISTANCE TO NONCOVALENT BTK INHIBITORS

Use of covalent or irreversible inhibitors of Bruton tyrosine kinase (BTK) in patients with chronic lymphocytic leukemia (CLL) has improved survival outcomes, but resistance can be acquired through mutation at the C481 residue, which impairs drug binding. Noncovalent or reversible BTK inhibitors have been developed that do not require C481 residue binding and therefore allow effective inhibition of C481-mutant BTK. However, knowledge of the mechanisms of resistance to noncovalent BTK inhibitors is lacking. Wang, Mi, Thompson, Mato, Taylor, Abdel-Wahab, and colleagues, therefore, investigated these mechanisms of resistance in nine patients with relapsed or refractory CLL treated with pirtobrutinib as part of the phase I/II BRUIN clinical trial. Using genomic analysis of patient samples from both pretreatment and time-of-progression time points, seven of the nine patients were found to have acquired new BTK kinase domain mutations outside of the C481 residue that were not present at the start of treatment. These mutations included V416L, A428D, M437R, T474I, and L528W, with no new C481 mutations being demonstrated. The remaining two patients presented mutations in the BTK downstream effector, PLCγ2. Functional characterization of these new non-C481 BTK mutations showed their association with resistance to multiple noncovalent BTK inhibitors by impairing drug binding. Examination on the effects of these mutations on BTK autophosphorylation, a marker of catalytic activity, revealed that these mutations diminished autophosphorylation, but downstream signaling was still activated. Furthermore, some of these mutations, including A428D and L528W, also conferred resistance to covalent BTK inhibitors. Therefore, this study demonstrates the mechanisms of resistance behind noncovalent BTK inhibitors and suggests the need to develop new therapeutic approaches to overcome this resistance, potentially through development of inhibitors targeting the scaffold function of BTK instead of its kinase function. Further analyses of a larger sample size as well as resistance mechanisms of previously untreated patients continue to remain necessary. ■

Wang E, Mi X, Thompson MC, Montoya S, Notti RQ, Afaghani J, et al. Mechanisms of resistance to noncovalent Bruton's tyrosine kinase inhibitors. N Engl J Med 2022;386:735–43.

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