Immunology

Major Finding: HPV+ head and neck squamous cell carcinomas exhibited diverse tumor-infiltrating B-cell subsets.

Concept: B cells in the tumor microenvironment were HPV antigen–specific and had signs of chronic exposure.

Impact: This study intricately characterizes B cells in these tumors and suggests how they may be harnessed.

HPV ANTIGEN–SPECIFIC B CELLS IN TUMOR MICROENVIRONMENT CHARACTERIZED

Although B cells and plasma cells are commonly found in the tumor microenvironment (TME), their roles have not been fully established, and whether they could be harnessed for anticancer therapies is unclear. To investigate this, Wieland and colleagues analyzed surgically resected samples from human papillomavirus (HPV)–positive head and neck squamous-cell carcinomas (HNSCC), first establishing that antibody-secreting cells in the TME produced HPV antigen–specific IgG antibodies, most often targeting the viral protein E2. Additionally, plasma titers of HPV antigen–specific IgG antibodies correlated with the presence of antibody-secreting cells specific to those antigens in the TME. Further analyses showed that the TME contained HPV antigen–specific activated B cells, a proliferating B-cell subtype committed to the memory B-cell lineage that was previously identified in the peripheral blood following vaccination or infection, a finding supporting the presence of chronic antigen exposure. Single-cell RNA-sequencing experiments revealed that the TME contained several types of antigen-experienced B cells, including antibody-secreting cells, activated B cells, and germinal center B cells. Overall, B cells (including activated B cells) were preferentially found in tumor stroma, where they formed clusters indicative of ongoing germinal center reactions, rather than the parenchyma. Similar trends in B-cell localization were observed in HPV-negative HNSCCs, but lymphocyte infiltration of these tumors was strikingly lower than that of HPV-positive HNSCCs. In summary, this work provides an intricate characterization of B cells in the TME of HPV-positive HNSCC, including their antigen specificity, and provides clues regarding how these B cells may be exploited for anticancer therapies. ■

Wieland A, Patel MR, Cardenas MA, Eberhardt CS, Hudson WH, Obeng RC, et al. Defining HPV-specific B cell responses in patients with head and neck cancer. Nature 2020 Nov 18 [Epub ahead of print].

Structural Biology

Major Finding: The small-molecule drug BI-3802 induced the formation of BCL6 filaments, leading to degradation.

Concept: Cryo-electron microscopy showed how BI-3802 facilitates BCL6 dimerization and assembly into helices.

Impact: This work reveals the mechanism behind a BCL6-degrading agent that may be of use in B-cell cancers.

BI-3802 PROMOTES POLYMERIZATION AND DEGRADATION OF ONCOGENIC BCL6

Targeting nonenzymatic oncogenic drivers such as BCL6, a transcriptional repressor that can promote B-cell malignancies such as diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma when mutated or dysregulated, has proven challenging. However, a recent screen for small-molecule BCL6 inhibitors revealed that BI-3802 could induce specific and potent ubiquitination and subsequent proteasomal degradation of BCL6 to a greater extent than other inhibitors or proteolysis-targeting chimeras (PROTAC). To determine the mechanism of BI-3802–mediated BCL6 degradation, Słabicki, Yoon, Koeppel, and colleagues began by establishing that BI-3802 was highly selective for BCL6 degradation and specifically depended on a region of 275 amino acid residues containing the BTB domain, which mediates BCL6's homodimerization and interactions with corepressors. Interestingly, treatment of cells derived from DLBCL cells with BI-3802 led to the reversible formation of BCL6 foci visible using live-cell fluorescence microscopy, suggesting that BI-3802 treatment may cause assembly of supramolecular BCL6 structures. Further investigation using negative-stain electron microscopy revealed that BI-3802 treatment triggered BCL6 polymerization into regular helical structures, and cryo-electron microscopy analysis was used to determine the structure of these filaments. Inspection of this structure revealed that BI-3802 was located at the interfaces between BCL6 dimers, where BI-3802 had specific contacts to a tyrosine residue in the BTB domain of one monomer and a cysteine residue in the BTB domain of the adjacent monomer while also facilitating the formation of an arginine–glutamate salt bridge between the two monomers. Mutating the BCL6 residues important for these interactions to alanine residues prevented the formation of BI-3803–induced BCL6 foci in cells, indicating that BCL6 polymerization is necessary for the appearance of these foci. CRISPR–Cas9-mediated genome-scale genetic screens revealed that the non-cullin E3 ubiquitin ligase SIAH1 was responsible for BI-3802–mediated BCL6 ubiquitination and degradation, with BI-3802 promoting interactions between SIAH1 and BCL6 as assessed through *in vitro* assays and in cells. Collectively, these findings clearly demonstrate the mechanism by which BI-3802 potently and selectively induces BCL6 degradation. ■

Słabicki M, Yoon H, Koeppel J, Nitsch L, Burman SSR, Di Genua C, et al. Small-molecule-induced polymerization triggers degradation of BCL6. Nature 2020;588:164–8.