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Voices

B cells and cancer

Tumor-infiltrating B cells complement T cell-mediated antitumor immunity. A panel of experts share their views on the complexity of B cells within the tumor microenvironment, the variety of mechanisms by which these cells control tumor growth, their organization in tertiary lymphoid structures, and their association with immunotherapy response.

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New views of B cells in cancer

The involvement of the immune system in eliminating incipient cancer cells and controlling tumor growth is no longer in question, but the focus has been on pro-inflammatory $CD8^+$ effector T cells, and the endogenous humoral immune response has largely been dismissed as a contributor. However, recent studies in humans have shown that intratumoral or peritumoral B cells are associated with positive prognosis and response to immunotherapy. These B cells are often organized into tertiary lymphoid structures (TLS), which are aggregates of immune cells with lymph node-like features and which have been proposed to establish a localized and sustained immune response. In some tumors, B cells in TLS form germinal centers and actively secrete antibodies that can recognize tumor-associated antigens.

Patients whose tumor-associated TLS contain germinal centers sometimes have better prognoses, and this reinvigorates the idea that endogenous humoral immunity contributes to tumor control. Alternatively, activated germinal center B cells may mark more robust T cell-mediated anti-tumor immunity, but they may not directly contribute to a therapeutic effect. Finally, our work has shown that B cells promote development of tumor-associated TLS through crosstalk with subpopulations of cancer-associated fibroblasts. These fibroblasts express molecules that promote B cell organization and survival, and the B cells promote local fibroblast proliferation and reticular organization. The field of cancer immunology is now confronted with an important opportunity to determine how any or all of these models apply in different tumor types, or in different patients, and to identify ways to utilize them therapeutically.

Jose R. Conejo-Garcia
H. Lee Moffitt Cancer Center and Research Institute

From villain to hero

Only through interdependent T cell and B cell interactions does adaptive immunity result in optimal memory antigen-specific responses. Although immuno-oncology remains T cell-focused, a flurry of recent papers consistently associates human cancer B cell infiltration with superior outcomes and enhanced T cell responses. Among the mechanisms whereby B cells promote anti-tumor immunity, their capacity to cross-present antigens to T cells has been independently suggested. This could be particularly important in TLS. B cells could also provide tonic signals to T lymphocytes, for instance, through ICOS ligand, CD80, or CD86. Besides, B cells produce isotype-switched antibodies that in some cases recognize extracellular domains on the tumor cell surface, thus re-directing the cytotoxic activity of natural killer (NK) and myeloid cells against tumor cells. Antibodies could also drive the uptake of dying tumor cells, thus exposing intracellular antigens via antigen presenting cells, or even neutralize exosomes. In addition, IgA transcytosis through $pIgR^+$ epithelial tumor cells sensitizes them to T cell-mediated killing. Finally, B cells produce cytokines that could create a microenvironment that is more permissive for effector T cells but hostile to tumor growth. The field urgently needs a better understanding of the role and assembly of TLS in order to elicit their formation in unresectable tumors. Equally important, elucidating the role of distinct antibody isotypes in different human tumors, and in particular the activity of IgA (and likely IgM) inside $pIgR^+$ tumor cells, could open

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new avenues for immunotherapies that finally target elicitation of coordinated cellular and humoral immunity.

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Harness both B and T cells

B cells and antibody responses have historically occupied the center stage in studies on infectious diseases and vaccines. However, there is now a consensus that both humoral and cellular immunity is critical in controlling infections. Cancer immunology is crossing the bridge from the other side—from a focus mostly on T cells during the past many years to the emerging interest in B cells. Recent studies have shown that intratumoral B cells are present in human cancer. This raises several key questions. The most important one is: What is the specificity of these B cells in the tumor—are they seeing cancer antigens expressed by the tumor? If so, are these antigens expressed on the surface of the cancer cell, or are they internal proteins? This has implications for treatment strategies using monoclonal antibodies for killing the cells and using bispecific antibodies for targeting the cancer cells. Will these cancer antigens recognized by B cells be common for a given type of cancer, or will they be distinct in different individuals irrespective of the type of cancer? How are B cell responses regulated during cancer—are there B cell-specific checkpoint inhibitors? What is the crosstalk between antigen-specific B and T cells in the tumor? It will be important to develop combination therapies that will synergize B and T cell interactions and enhance both humoral and cellular responses against the tumor. Optimal cancer immunotherapy may well require harnessing both arms of the adaptive immune system. The rules of cancer immunology and infectious disease immunology have much in common.

Brad H. Nelson
BC Cancer Victoria

Bending self-tolerance

Early studies in mice have indicated that B cells can inhibit anti-tumor immunity; however, the strong prognostic and predictive impact of tumor-infiltrating B cells (TIL-B) in human cancers implies the opposite. Undoubtedly TIL-B can adopt a regulatory phenotype under certain conditions, but this appears to reflect a phenotypic state rather than hard-wired lineage. Indeed, in single-cell sequencing datasets from human tumors, $CD4^+$ Tregs are obvious, but Bregs remain elusive. Even IL-10, the most commonly reported Breg effector molecule, can be immunostimulatory in some contexts.

Effector TIL-B populations show hallmarks of antigen recognition, including antibody class switching and somatic hypermutation, often giving rise to extensive phylogenies with broad anatomical distributions. The TIL-B target antigens that have been identified so far are primarily non-mutated proteins with broad or even ubiquitous expression patterns, and this suggests that TIL-B responses reflect a breakdown in peripheral tolerance rather than classic adaptive immunity.

This may be a critical clue to how the immune system combats intratumoral heterogeneity. Anti-tumor immunity might be initiated by T cells recognizing tumor-specific antigens (e.g., neoantigens), but through B cell-mediated antigen spreading, the response could broaden to include self-antigens that have a more ''truncal'' expression pattern on tumors and are less susceptible to immune editing. If B cells do indeed generate a type of autoimmune response in tumors, then a big question for the field becomes: What mechanisms keep these responses focused on tumor tissue?

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Active versus inactive TLS

TIL-B in human tumors are frequently nominal, and a significant population is detected in only 10–20% of breast cancers. When they are abundant, TIL-B are predominantly resident in TLS, which are ectopic lymphoid formations that can develop in the tumor microenvironment (TME). $CXCR5^+$ TIL-B, together with $CXCR5^+CD4^+$ and $CXCR5^+CD8^+$ T cell TIL, are recruited by CXCL13, a chemokine that plays a central role in TLS formation. Importantly, tumor-associated TLS do not automatically reflect active anti-tumor immunity, and data show that only TLS with germinal centers are functional. Active TLS are distinguished by proliferating germinal center TIL-B, functional Th1-oriented T follicular helper (Tfh) TIL, functional T follicular regulatory (Tfr) TIL, and activated cytotoxic T cell TIL. Their collective cell-to-cell interactions and soluble factor secretion drive anti-tumor cellular and humoral immune responses in active TLS in a way that is similar to events in secondary lymphoid organs. High-affinity antibody maturation and IgG1/IgG3 isotype-switching in TLS are linked with antibody-dependent cellular cytotoxicity (ADCC)-mediated tumor cell killing, while other isotypes are more frequently associated with pro-tumor or suppressive responses. TIL-B in TLS may also function as antigen-presenting or regulatory cells, thereby directly regulating some T cell responses. The majority of $PD\text{-}1^+/PD\text{-}L1^+$ cells in most breast tumors reside in TLS, and frequent contacts between $PD\text{-}1^+$ Tfh TIL and $PD\text{-}L1^+$ TIL-B or macrophage-lineage cells suggest that they are a major target for immune checkpoint inhibition (ICI). Disruption of the PD-1/PD-L1 immunosuppressive pathway in active TLS and potential restoration of functionality in inactive TLS may be triggering the regeneration of anti-tumor immunity in patients who respond to immune checkpoint blockade. Although studies link tumor-associated TLS with better clinical outcomes, the significance of active versus inactive TLS remains a key open question.

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TLS maturation

Novel immune targets are critically needed to further improve ICI. Although T cells centrally mediate anti-tumor immunity, B cells partner with T cells in TLS to enhance anti-tumor immunity and improve patient outcomes. However, little is known about the link between B cell subsets and/or function and TLS in the TME.

Organization of immune cells into distinct cellular neighborhoods like TLS is critical for B cell function in tissues. Evidence from normal lymphoid tissues demonstrates that cellular neighborhoods are vital for this process because a lack of secondary lymphoid organs diminishes B and T cell function.

We postulate that B cell subsets and/or function is correlated to TLS composition. B and T cells are not in clearly defined neighborhoods during early TLS formation. Thus, naive B and T cells are more abundant with downstream activation of B cells. Moving from an early TLS to a mature TLS with a secondary follicle, germinal center and memory B cells emerge, aided by T follicular helper cells, leading to long-lived plasma cells (PCs). Mature TLS harbor B cells that function as tumor-specific antibody producers and antigen presenters. Without TLS, B cells function suboptimally and can become suppressive. Finally, B cell subsets and TLS maturity may correlate with patient prognosis and ICI response, and B cells within TLS are more beneficial. We are testing these knowledge gaps in order to improve B cell-targeted immunotherapies for cancer patients.

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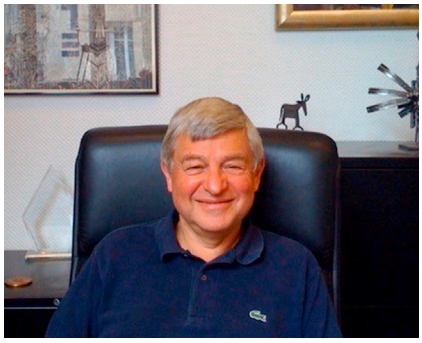

Wolf H. Fridman
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Tumor control by B cells

Although the impact of T cells in controlling cancer progression is well established, and it has led to the development of immunotherapies that aim to reinvigorate T cells through targeting immune checkpoint molecules in the TME, the role of B cells has, until recently, been underestimated. However, in most cancer types, B cells are present at different locations and densities in the TME. Most are in TLS within germinal centers in which they undergo a full maturation process from naive B cells to memory B cells and PCs which propagate into the tumor bed. B cells can present antigens to T cells either directly or via immune complexes that are endocytosed by dendritic cells. This amplification loop is particularly effective in poorly immunogenic tumors which are unable to directly activate T cells. Antibodies produced by PCs may also promote anti-tumor effector functions of macrophages and NK cells. In contrast, in tumors with immature TLS that lack a germinal center, B cells adopt a regulatory phenotype and inhibit immune reactions. Immune complexes may also activate complement or macrophages to fuel pro-tumoral inflammation. The roles of B cells are therefore complex, depending on the nature of the antigens they recognize and the composition of the TME. In conclusion, the density of B cells and mature TLS is a major predictor of response to immunotherapy, and this allows us to extend its field to poorly immunogenic tumors.