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EDITORIAL

Form Follows Function for Local Immune Responses in Pancreatic Cancer

Immunotherapy research has been making profound advances in treatment of some malignancies, such as melanoma, yet cancers such as pancreatic ductal adenocarcinoma (PDAC) remain largely refractory to these therapies. It has become apparent that the presence of scattered lymphocytes and antigen-presenting cells within the tumor microenvironment is not sufficient to mount an effective cytotoxic immune response. Rather, these cells must form complex lymphoid structures within the tumor microenvironment for function. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Delvecchio et al[1] uncover mechanisms by which tumors develop these structures and how they can be targeted for more effective therapies.

Although canonical cytotoxic immune responses involve antigen-presenting cells recognizing antigens and trafficking them to lymph nodes for T-cell activation, recent work suggests that activation in PDAC requires the presence of local lymphoid structures. Approximately one-third of PDAC patients have tertiary lymphoid structures (TLSs), also known as tertiary lymphoid tissue, within the tumor microenvironment. These TLSs are composed of aggregated lymphocytes and dendritic cells organized with follicle-like structure and the presence of germinal centers. The abundance of these TLSs correlates with prognosis in PDAC patients; Castino et al[2] found that a high density of B cells localized to tertiary lymphoid tissue correlated with better patient survival, whereas a high density of scatteringly infiltrating B cells did not correlate with better survival.

To understand how these TLSs work and how they can be manipulated for better clinical outcomes, Delvecchio et al[1] turned to mouse models of PDAC, comparing autochthonous tumors (arising in mice genetically engineered to express mutations in *Kras* and *Trp53*) with engraftment of syngeneic tumor cells into the pancreas. They found that autochthonous tumors developed TLSs in almost half of mice, similar to the prevalence seen in humans. However, the engrafted tumors did not develop TLSs. Even though some of the engrafted tumors recruited relatively high densities of T and B lymphocytes, they failed to form the structure of mature TLSs. Building on knowledge from human TLSs, Delvecchio et al[1] injected engrafted tumors with CXCL13 and CCL21 and found that this induced TLS development in almost half of mice, a proportion similar to that occurring in autochthonous mouse tumors. This chemokine-mediated induction of TLSs combined with gemcitabine treatment resulted in smaller tumors than seen with gemcitabine alone.

In human patients and the mouse models described, TLS development was not universal. Even in genetically identical mice engrafted with the same cell line, injection of CXCL13 and CCL21 was sufficient to induce TLSs in only half of mice, suggesting that the presence of TLSs may not be caused by the genetics of the patient/mouse or the tumor itself in every case. The model system developed by Delvecchio et al[1] necessitates injection-induced damage for the administration of chemokines. Injection of phosphate-buffered saline alone induced elevated lymphocyte numbers but without the structure necessary for mature TLS function. This raises the possibility that TLS formation in response to these chemokines may also depend on a damage response induced by injection itself. The pancreas is an organ exquisitely attuned to mitigating damage. Because acinar cells contain potentially destructive digestive enzymes, the pancreas has developed surveillance and response pathways that rapidly induce fibrosis and immune responses following perceived damage. Because PDAC is so seldom detected in early stages, we have little idea of how its development varies from one patient to another. Although fibrosis and a robust macrophage response are nearly universal in both chronic pancreatitis and PDAC, it is possible that differences in the extent of damage or the type of damage that occurs as tumors develop may impact other immune responses, such as TLS development.

The work by Delvecchio et al[1] creates several important advances in the field. First, they identified a model to pursue the underlying causes of TLS development in some patients but not in others. Second, they have developed a model system to determine how TLSs function in the immune response of PDAC. Third, their model will allow assays to determine how best to induce an antitumor immune response in patients who have TLSs. For example, they can test various therapies including immunotherapies to determine if the presence of TLSs is sufficient for an antitumor response or if these therapies must be combined with other therapies, such as those inducing neoantigen responses.

The increasing understanding of how to harness cytotoxic immune responses for more effective anticancer therapies provides stronger rationale for further research and greater hope for patients. Models such as described here are critical to continue this exponential trajectory.

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Conflicts of interest
The author discloses no conflicts.


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