Tumor Landscapes: β-Catenin Drives Immune Desertification

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In this issue of Clinical Cancer Research, Luke and colleagues tested the universality of the tumor-intrinsic WNT/β-catenin pathway in driving immune desertification in cancer by mining The Cancer Genome Atlas (TCGA) pan-cancer database (1). Efficient immune recognition can indeed control tumor outgrowth both in animal models and in human patients. On the basis of the presence of preexisting T-cell immune responses, tumors have been categorized as immunogenic, in the presence of preexisting T-cell immune responses, tumors have been categorized as immunogenic, inflamed, or hot tumors and nonimmunogenic, noninflamed, or cold tumors. Definitive proof for the ability of tumor-infiltrating T cells (TILs) to eliminate human tumors is given by the clinical responses following adoptive transfer of ex vivo–expanded autologous TILs, and by the numerous clinical responses in patients treated with antibodies neutralizing the programmed death 1 (PD-1) pathway.

What leads to the establishment and persistence of spontaneous antitumor T-cell responses remains partly unclear. Recent literature suggests that tumorigenic cancer cell–intrinsic pathways can shape and regulate TIL infiltration. For example mutations in the DNA repair pathway, microsatellite instability, and POLE mutations, which generate genomically unstable tumors, are characterized by a higher T-cell content. Tumors with mismatch-repair deficiencies respond better to immune checkpoint blockade (ICB) comparing to mismatch-proficient tumors. On the contrary, gain-of-function alterations of the WNT/β-catenin or MYC pathway, and loss-of-function mutations in PTEN or loss of the LKB1 pathway restrain T-cell recruitment and generate non-inflamed tumors. Inhibition of the above oncogenic pathways via genetic manipulation in mouse models has sensitized tumors to ICB, while tumor types resistant to immunotherapy like paraganglioma, uveal melanoma, and adrenocortical tumors had the highest proportion of non-T-cell–inflamed cases. Metastatic melanoma, with an approximate 40% objective response rate to ICB, displayed a similar proportion of hot tumors. Importantly, comparing matched tumor and normal adjacent tissues they found that cold tumors of most tumor types analyzed (except kidney cancer) displayed lower levels of the T-cell infiltration. For example mutations in the WNT/β-catenin tumor-intrinsic signaling is emerging as an immune exclusion pathway that holds high promise to counteract resistance to immunotherapy.

Prompted by their previous seminal findings in melanoma, where gain of function in the WNT/β-catenin pathway drives exclusion of CD103+ dendritic cells and antigen-specific T cells (2), they next assessed cold solid tumors for alterations in the WNT/β-catenin pathway. Fifteen percent of the cold tumors and 10% of the hot tumors were enriched for gain-of-function mutations and copy number alterations. Although this difference in enrichment was faint, it was found to be statistically significant. The vast majority of these alterations were dominated by activating mutations in CTNNB1 and APC loss from colorectal cancers. These results suggested that DNA alterations in WNT pathway are not frequently implicated in mediating immunosuppression. Then, they computed β-catenin activity scores using gene expression signatures of known cancer type–dependent CTNNB1 transcriptional targets and evaluated their enrichment across hot and cold tumors. Approximately half of the cancer types had high β-catenin scores within cold tumors. Cancers like clear cell kidney carcinoma, adrenocortical, sarcoma, and ovarian cancers had the highest β-catenin enrichment difference (at least 47%) between noninflamed and inflamed tumors. However, these differences often only involved a few patients. Colorectal cancer and melanoma had an extensive overlap between inflamed and noninflamed tumors in the β-catenin gene expression score. Finally, CTNNB1 protein levels anticorrelated with the T-cell–inflamed score in 65% of cancer types. In summary, 90% of cancer types displayed higher β-catenin activity in cold tumors, which could be attributed to either (1) DNA alterations.
of WNT-related genes, (ii) hyperactivation of the WNT/β-catenin pathway, or (iii) CTNNB1 protein overexpression. All three parameters could be identified in approximately 29% of cases, and the molecular basis of WNT/β-catenin–mediated exclusion of T cells in cold tumors is illustrated in Fig. 1.

Transcriptional profiling of bulk tumors combined with bioinformatic analyses permits the assessment of both the tumor and stroma components of cancer and has been widely used to unravel predictive gene expression signatures. Most methods computing gene signature scores utilize gene-set enrichment analysis (GSEA), utilize gene-set variation analysis (GSVA), or compute the mean or median expression of individual genes. Luke and colleagues performed a score categorization for the expression of each gene (i.e., +1 for downregulated, 0 for nonvarying, and +1 for upregulated) and further categorized their resulting sum. This signature correlated tightly to established scores reflecting T-cell cytotoxicity. However promising, the lack of standardization of reported signatures with respect to gene content and how they are computed has made their clinical application challenging so far.
Although purely in silico and lacking experimental validation across tumors, the work by Luke and colleagues introduces an important concept, that of identifying cold tumors by measuring the activity of tumor-intrinsic pathways such as WNT/β-catenin. However, how universally active and dominant the WNT/β-catenin pathway is in noninflamed tumors requires further investigation. The authors show that only a proportion of noninflamed tumors display activation of the WNT/β-catenin pathway, suggesting that other tumor cell–intrinsic pathways could contribute to immune desertification. Additional parameters such as the presence of immunogenic epitopes and the level of DNA damage might, for example, be also at play, diluting the effect of the WNT/β-catenin pathway on immune desertification.

It is well established that the metastatic process requires WNT/β-catenin activity for epithelial–mesenchymal transition, cell proliferation, and angiogenesis. Thus, the results of Luke and colleagues, may underestimate the actual prevalence of the WNT/β-catenin pathway, because the authors mainly analyzed TCGA data, which almost exclusively contains primary tumor data. Tumors with high mutational load and preserved truncal mutations are more likely to respond to ICB than highly heterogeneous tumors. Furthermore, intratumoral heterogeneity (ITH) can lead under continuous pressure by local factors, the immune attack, and applied therapies to important clonal divergence. One could hypothesize that more than one tumor-intrinsic pathway can thus emerge stochastically in distinct metastatic sites, independently leading to immune desertification. The aspect of ITH is often overlooked and cannot be accurately addressed by the TCGA as its data are derived from single tumor sites. The study by Jiménez-Sánchez and colleagues (3), looking at multiple metastases of ovarian cancer before and after chemotherapy suggests that indeed WNT but also the MYC pathway seem to dominate the immune desertification process at metastatic sites, further underscoring the significance of the findings by Luke and colleagues.

In conclusion, understanding the causal relationship between the genetic makeup of tumors and immune landscape has important implications for patient stratification for immunotherapy, understanding resistance to it, and for prioritizing pathways for development of drug combinations.

Disclosure of Potential Conflicts of Interest
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