CCBIO Opinion

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THE PROMISE OF PATIENT SELECTION IN TARGETING THE TUMOR MICROENVIRONMENT

The tumor microenvironment (TME) is a catch phrase that encompasses many aspects of tumor biology. Solid tumors consist of many cell types (e.g., tumor cells, immune cells, fibroblasts, endothelial cells) and an extracellular matrix that comprise the TME. Investigations into cell-cell communication and how cells in the tumor interact with and alter their local surroundings all fall under the umbrella of TME research. In general, an improved understanding of how the many facets of the TME contribute to tumor development and progression has elevated our ability to detect, diagnose and treat tumors. In fact, "targeting the TME" has become the strategy of the day in terms of developing new anti-cancer therapies. One needs to look no further than the explosion in therapeutic strategies that aim to harness the power of the immune system for cancer therapy. Immune oncology approaches capitalize on the TME by altering signaling between tumor cells and the microenvironment to facilitate immune recognition and immune-mediated destruction of tumor cells.

A particularly potent immune oncology strategy is immune checkpoint blockade (ICB). Immune checkpoints are evolutionarily conserved "OFF" signals designed to constrain the duration and amplitude of T cell-mediated immune responses to reduce collateral tissue damage and maintain self-tolerance. Tumors hijack immune checkpoints as a major strategy to avoid immune surveillance. Thus, blockade of immune checkpoints can release tumor antigen primed T cells to attack tumor cells. This has been effective in a subset of cancer patients; however, a significant portion of cancer patients do not benefit or only have partial or short-term responses. The "rules" that dictate response to ICB are being re-evaluated on a regular basis but it is clear that tumor antigen primed effector T cells are required for ICB to be effective.

Appropriately primed effector T cells are often lacking in solid tumors. This is due in part to the TME, in which there are many mechanisms, pathways and cell types that induce and maintain an environment that suppresses the development and recruitment of primed effector T cells. Thus, targeted agents that inhibit TME-related signaling are being combined with ICB in preclinical and clinical studies. However, given the numerous TME associated pathways that can contribute to the deficit of effector T cells, it is unlikely that a single TME pathway or target will have broad spectrum efficacy in combination with ICB.

An attractive idea is to identify patients based on *oncogenotype* and pair TME-targeted therapy with an appropriate ICB based on biology. Two examples from our preclinical experience follow. First, transforming growth factor β (TGFβ) is a major driver of immune suppression and epithelial plasticity and consequently is an attractive therapeutic target in many solid tumors. However, TGFβ is also a tumor suppressor. As a result, blocking TGFβ has not been effective preclinically or clinically thus far in unselected patient populations. Importantly, mutations in the canonical TGFβ signaling cascade are common in some cancers. For instance, loss of TGFβ receptor 2 or Smad4 occurs frequently in pancreatic cancer. We found that *TGFβ receptor 2-deficient* pancreatic tumor cells form tumors that are sensitive to TGFβ inhibition (Huang et al., 2019). Current unpublished studies support that pancreatic tumors that are *Smad4-deficient* also respond positively to TGFβ blockade. Efficacy in each case is

due to the direct effect of TGFβ blockade on the TME. Furthermore, inhibition of TGFβ in these TGFβ-signaling deficient tumors results in a substantial change in the tumor immune landscape portending an improved response to ICB. These observations suggest that patients with a deficiency in canonical TGFβ signaling should be considered for TGFβ inhibition while patients that are wild-type for TGFβ signaling should not be enrolled in studies that exploit a TGFβ-targeting strategy. A second example of targeting a TME pathway in a distinct oncogenotype can be drawn from studies performed in *LKB1/Stk11* mutant lung cancer, an oncogenotype that is typically refractory to ICB. Inhibition of the receptor tyrosine kinase AXL on stromal cells, in particular dendritic cells, facilitates the development of tumor antigen primed effector T cells resulting in tumor sensitivity to ICB. AXL can also be expressed on the tumor cell but does not appear to be relevant to the increase in response to ICB in this scenario; highlighting that TME associated AXL is the critical target (Li et al., 2022).

These examples demonstrate the utility of linking tumor cell oncogenotype to distinct TME-targeting strategies. Molecular characterization of patient tumors is becoming routine in the clinical decision tree of cancer care. Understanding how particular oncogenotypes influence the TME should be the next wave of TME research. To that end, a recent study on a novel $Kras^{G12D}$ inhibitor, MRTX1133, demonstrates that efficacy in pancreatic cancer models relies on T cells (Kemp et al., 2023). These data suggest that combining MRTX1133 with the appropriate TME-targeted agent has the potential to provide long-term benefit in a historically recalcitrant tumor. Until recently, "targeted therapy" has been limited to pharmacologic inhibition of specific alterations in tumor cells. It is time to broaden that definition to include identifying targets in the TME of selected patients. Linking distinct oncogenic drivers to TME-associated, pharmacologically targetable vulnerabilities is a significant undertaking, but has the potential to deliver the next wave of precision medicine: patient selection for rationally designed combination therapy. ••

References

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