Abstract for Virtual Frontiers in Cancer Science 2020 - Singapore

Targeting the Tumor Microenvironment

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Targeting immune suppression mechanisms has revolutionized cancer treatment in recent years. While immune checkpoint inhibition has yielded meaningful responses across many cancer types, clinical trials have shown eventual treatment resistance, and in some cancers (e.g., prostate) minimal therapeutic response at all. Our recent work has identified symbiotic interactions between cancer cells and the host tumor microenvironment (TME) in regulating immunity and metabolism, thus providing new candidate therapeutic targets for intractable disease. Here we highlight some of our findings: (1) Paracrine signaling in the tumor microenvironment plays a key role in the oncogenic KRAS-driven metabolic reprogramming of pancreatic cancer cells. Specifically, type II cytokines, secreted by Th2 cells in the tumor microenvironment, can stimulate cancer cell-intrinsic MYC transcriptional upregulation to drive glycolysis. (2) We explored mechanisms involving the TME as a potential basis for resistance to targeting KRAS in pancreatic cancer. Although oncogenic KRAS is required for pancreatic tumor maintenance, tumors can recur following KRAS extinction. We found that pancreatic cancer cells can alter the TME myeloid cell composition to support oncogenic KRAS-independent tumor growth. (3) We also sought to understand the essential role of CHD1 in PTEN-deficient prostate cancer. We determined that CHD1 deletion causes major remodeling of the TME, and established CHD1/IL-6 as a major regulator of the immunosuppressive TME in PTEN-deficient prostate cancer. These observations of cancer cell/immune cell crosstalk across cancer types open the possibility of new strategies to enhance the effectiveness of current immune cell inhibitor therapies by combination with TME-targeted therapies.