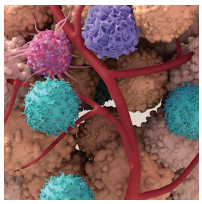
Tumor Microenvironment

Major Finding: The microenvironment influences cancer transcriptional state and drives drug response.

Concept: Comparison of metastatic biopsies and matched organoids determined environmental control of transcriptional heterogeneity.

Impact: The developed framework provides insight into drivers of cancer cell state and their impact on drug response.

TUMOR MICROENVIRONMENT INFLUENCES CANCER CELL TRANSCRIPTIONAL STATE



Despite the existence of single-cell RNA sequencing (scRNA-seq)–derived transcriptional maps of cancer, the influence cell-intrinsic and cell-extrinsic factors have on cancer cell state remains to be fully elucidated. Raghavan, Winter, Navia, Williams, and colleagues developed and utilized a high-resolution platform to profile metastatic tissue and matched organoid models from patients with pancreatic cancer using scRNA-seq to show that, although genomic alterations were conserved between tumors and cancer models, the same was not always true for RNA signatures. The programs derived from the single-cell cohort of metastatic disease samples were denoted as single-cell basal (scBasal) or single-cell classical (scClassical). These states were not mutually exclusive and could be coexpressed by individual cells, leading to a third subset, the intermediate coexpressor (IC) state, which demonstrated a distinct 115-gene signature. Investigation into separation between biopsy and corresponding organoid transcriptional profiles indicated divergence with robust loss of the scBasal gene signature in some organoids, and to a lesser extent the IC program, while the scClassical signature remained relatively preserved, suggesting that microenvironmental factors could induce the observed gene expression program changes. To investigate how this selection and plasticity occurs, organoids were grown in minimal media lacking serum and mitogens, which caused a shift toward a more scBasal or IC state, while organoids in typical growth-stimulating media exhibited an scClassical expression pattern. However, this did not fully recapitulate the polarization observed *in vivo*, supporting the critical role of factors within the tumor microenvironment (TME) in dictating cell state. Furthermore, TME composition was determined to be more diverse in scClassical or IC expression patterns, while scBasal-classified tumors had a more homogenous TME, with differentially expressed secreted factors being responsible for driving malignant cell state. Shifts in cancer cell state in response to TME signals were also able to alter drug response. This study provides insight into cancer cell transcriptional states as well as their plasticity and functional significance, which could eventually support targeting cell state to improve therapeutic response. ■

Raghavan S, Winter PS, Navia AW, Williams HL, DenAdel A, Lowder KE, et al. Microenvironment drives cell state, plasticity, and drug response in pancreatic cancer. Cell 2021;184:6119–37.e26.

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Immunology

Major Finding: High NRP1 surface expression can lead to more suppressive T_{regs} and reduces progression-free survival.

Concept: T_{regs} in the absence of activation or in noncancer tissues do not express high surface levels of NRP1.

Impact: The targeting of NRP1 represents a therapeutic option in reducing immunosuppression.

SURFACE EXPRESSION OF NRP1 ON T_{regs} AFFECTS OUTCOME IN PATIENTS WITH CANCER

The immunosuppressive tumor microenvironment represents a major obstacle to therapeutic response, with regulatory T cells (T_{reg}) playing a critical role. T_{regs} have proven difficult to target due to ensuing peripheral autoimmunity; therefore, Chuckran and colleagues investigated the role of neuropilin-1 (NRP1) on T_{reg} function in cancer, as it has been previously shown in mouse tumor models to be a key intratumoral functional regulator of T_{regs} but dispensable for peripheral homeostasis. Using 375 samples from patients spanning 6 different cancer types and 85 healthy controls, T_{regs} from patients with solid cancers demonstrated higher NRP1 surface expression ($NRP1^{SURF+}$) as compared with site-match noncancer tissue. Individuals with head and neck squamous cell carcinoma (HNSCC) who displayed a high proportion of $NRP1^{SURF+}$ T_{regs} had reduced progression-free survival and disease-specific survival at 3 years. Furthermore, an increase in the proportion of activated T_{regs} was seen in the $NRP1^{SURF+}$ population which were more stable and expressed higher levels antiapoptotic and proliferation markers. Additionally, these $NRP1^{SURF+}$ T_{regs} were more suppressive in both HNSCC and ovarian cancer tumors, and this effect was diminished upon use of an NRP1 blocking antibody. IL2 treatment in conjunction with stimulation of the T-cell receptor *in vitro* led to an upregulation of $NRP1^{SURF}$ after 6 days but was not observed at day 3, supporting this as a late activation event. Treatment of these T_{regs} with MAPK inhibitors targeting MEK1/2 or ERK1/2 inhibited $NRP1^{SURF}$, indicating that this pathway plays a role the regulation of NRP1 expression. Moreover, expression of NRP1 is both elevated and detectable in peripheral blood lymphocytes of patients with cancer and correlates with intratumoral expression, suggesting its use as a blood marker of poor prognosis. Overall, this study implicates a role of NRP1 and its surface expression in T_{reg} function in multiple cancer types as well as its effects on patient outcome and establishes a basis for future clinical evaluation of modulators to T_{reg} stability and function in cancer. ■

Chuckran CA, Cillo AR, Moskovitz J, Overacre-Delgoffe A, Somasundaram AS, Shan F, et al. Prevalence of intratumoral regulatory T cells expressing neuropilin-1 is associated with poorer outcomes in patients with cancer. Sci Transl Med 2021;13:eabf8495.

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