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Coordinated multicellular programs in the colorectal cancer microenvironment

Tumors are complex ecosystems shaped by both the identity and spatial organization of diverse cell types. Understanding how these factors evolve during cancer progression may help reveal coordinated multicellular behaviors linked to disease outcome. In this study, we profiled 522 colorectal samples using multiplexed ion beam imaging (MIBI-TOF) and a 42-marker panel capturing cell lineage, function, and metabolism. Over 488,000 cells were analyzed to map cellular neighborhoods and metabolic states across disease stages.

We observed metabolic heterogeneity in healthy to malignant samples. Aggressive cancer cells showed malignant adaptation beyond their proliferative state with increased amino acid and oxidative phosphorylation metabolism. Tissue architecture remodeling also tracked with disease progression. Cell composition shifted with increasing tumor stage, including gains in myeloid cells and losses in lymphocytes. Some spatial relationships between cell types were specific of tumors, particularly among macrophages, neutrophils, and fibroblasts. Using machine learning, we identified spatial and molecular features that most strongly predicted tumor stage, such as presence of monocyte clusters.
Finally, a factor analysis framework revealed coordinated shifts in spatial, morphological, and metabolic programs, with distinct cell-type contributions at early versus late stages. These coordinated multicellular programs were strongly associated with clinical variables such as tumor and node invasion stages and microsatellite instability.

Our ongoing work aims to integrate these spatial and metabolic features into predictive models of tumor behavior. Our cross-validation effort suggests spatial lineage and metabolic interactions outperform single-feature predictors. This study supports the view that tumor progression is governed by coordinated multicellular programs, and highlights interpretable features that may inform patient stratification or therapeutic targeting.

Research type

Translational research

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