Ex-vivo Modeling of Metabolic Niches to explore Tumor-Immune Interactions in CRC patient-derived Organoids

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Metabolic heterogeneity within the tumor microenvironment profoundly shapes immune responses and contributes to disease progression, yet ex-vivo model systems to study these interactions in a human context remain limited. Here, we establish a patient-derived colorectal cancer organoid platform to dissect the role of metabolic niches in regulating immune cell function. Using CRISPR/Cas9 technology, we introduce targeted knockouts in key metabolic pathways to generate organoids with distinct metabolic phenotypes.
These organoids are co-cultured with macrophages, central regulators of inflammation and tissue remodeling, whose phenotype and function are tightly regulated by metabolic cues within the TME. In colorectal cancer, macrophages can polarize toward pro-inflammatory, glycolysis-dependent M1-like states that support anti-tumor immunity or toward oxidative phosphorylation– and fatty acid oxidation–dependent M2-like states associated with immunosuppression and tumor progression, which is highly influenced by nutrient competition and metabolite availability in the TME. Our model enables the systematic investigation of how tumor-intrinsic metabolic alterations modulate macrophage activation states, metabolic reprogramming, and effector functions. This metabolic niche model system provides a controlled ex-vivo framework to explore the crosstalk between cancer cell metabolism and the immune compartment, with the potential to reveal novel mechanisms of immune regulation and therapeutic vulnerabilities.