Metabolism

Major Finding: Myeloid cells in the tumor microenvironment exhibited the highest uptake of intratumoral glucose.

Concept: Immune cells relied on glucose metabolism, whereas cancer cells preferentially consumed glutamine.

Impact: This work shows that cell-intrinsic programs control differences in nutrient metabolism in the TME.

CELL-INTRINSIC PROGRAMS PARTITION NUTRIENTS IN TUMOR MICROENVIRONMENT

Tumor cells often rely on aerobic glycolysis, in which cells metabolize glucose to lactate in the presence of oxygen. Based on this characteristic, positron emission tomography (PET) using a radiolabeled glucose analogue has become a standard technique enabling the clinical detection and monitoring of tumor progression. Similar to cancer cells, immune cells in the tumor microenvironment (TME) also rely on glucose metabolism. To investigate whether immune cells and cancer cells may compete for access to nutrients, Reinfeld, Madden, and colleagues used PET to assess the uptake and metabolism of glucose across various cell subsets in the TME. Following *in vivo* administration of radioactive glucose analogue ^{18}F-fluorodeoxyglucose (FDG) in multiple syngeneic murine tumor models, tumor-infiltrating CD45$^+$ immune cells displayed a significantly greater uptake of FDG per cell than CD45$^-$ cancer cells did. Fractionation of the TME into various immune subsets revealed that CD11b$^+$ myeloid cells took up significantly more glucose than CD4$^+$ or CD8$^+$ effector T cells or CD45$^-$ cancer cells. Specifically, monocytic myeloid-derived suppressor cells and tumor-associated macrophages were two myeloid populations that contributed to high glucose consumption, and both populations were enriched with transcripts associated with glucose-related pathways. When mice were treated with rapamycin to inhibit mammalian target of rapamycin complex 1 (mTORC1), known to promote anabolism and nutrient uptake, both immune cells and cancer cells exhibited decreased FDG uptake. To investigate whether glutamine, like glucose, was also partitioned between specific cell subsets in the TME, a glutamine radiotracer was administered to tumor-bearing mice and shown to preferentially partition into CD45$^-$ cancer cells. When glutamine transport was inhibited pharmacologically, the uptake of glucose was increased in all TME cell subsets. Together, this work suggests that glutamine metabolism inhibits glucose metabolism and supports a model in which cell-intrinsic, mTORC1-driven programs dictate preferential glucose and glutamine metabolism in immune cells and cancer cells, respectively, in the TME. ■

Reinfeld BI, Madden MZ, Wolf MM, Chytil A, Bader JE, Patterson AR, et al. Cell-programmed nutrient partitioning in the tumour microenvironment. Nature 2021;593:282–8.

Structural Biology

Major Finding: Oncogenic receptor tyrosine kinase fusions assembled into functional cytoplasmic protein granules.

Concept: These granules, lacking membranes and RNA, activated the RAS pathway and other signaling pathways.

Impact: This suggests the existence of an alternate, membrane-free platform that can initiate RAS signaling.

RTKs CAN FORM MEMBRANELESS GRANULES TO DRIVE CYTOPLASMIC RAS SIGNALING

Although it is generally accepted that activation of receptor tyrosine kinase (RTK) RAS-family GTPases and the consequent downstream MAPK signaling requires RTK and RAS protein association with a lipid membrane, recent studies have demonstrated that the fusion oncoprotein EML4–ALK, a chimera of the ALK (an RTK) kinase domain with a fragment of the protein EML4, is not found at the plasma membrane but instead exists in cytoplasmic structures of unknown identity. In light of these findings, Tulpule, Guan, Neel, and colleagues sought to better understand the nature of these structures and determine how EML4–ALK can activate oncogenic RAS signaling, potentially without membrane association. Experiments using the most common oncogenic EML4–ALK fusion protein (variant 1) in human cancers revealed the presence of EML4–ALK in protein-based cytoplasmic granules lacking RNA and lipid membranes and unperturbed by membrane-solubilizing agents, and although these granules were heterogeneous in biophysical nature, most exhibited solid-like properties. Further analysis showed that these EML4–ALK granules were capable of recruiting the RAS-activating ternary complex GRB2–SOS1–GAB1, which locally activated RAS proteins. Not only were these protein granules sufficient to activate downstream RAS signaling, but their formation was also necessary for EML4–ALK-mediated RAS signaling. Further, the formation of large, higher-order EML4–ALK-containing protein granules was essential for RAS–MAPK pathway activation in this context, whereas the presence of smaller multimers was not sufficient. Deeper investigation using additional RTKs suggested that signaling via membraneless protein granules may be a generalizable means of oncogenic chimeric RTK–driven RAS pathway activation distinct from known pathways involving membrane-associated RAS proteins. Collectively, these findings imply that phase-separated protein granules may underlie a unique mechanism of oncogenic RTK and RAS pathway activation, both common cancer drivers. ■

Tulpule A, Guan J, Neel DS, Allegakoen HR, Lin YP, Brown D, et al. Kinase-mediated RAS signaling via membraneless cytoplasmic protein granules. Cell 2021 Apr 12 [Epub ahead of print].