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Metabolism shapes the tumor microenvironment

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Tumors are strongly influenced by the surrounding normal tissue, which forms a specialized niche termed the tumor microenvironment (TME). The TME is modeled by cancer cells for their own benefit through a complex array of interactions. The identification of new forms of communication within the TME, which are dependent on the tumor's metabolic activity, has expanded our understanding of this heterocellular regulation and has revealed potential therapeutic targets. This review will summarize recent findings on the metabolic regulation of tumor cells by the TME. The concepts to be discussed include the existence of metabolic intratumoral heterogeneity, the contribution of cancer associated fibroblasts (CAFs) to tumor progression, and the regulation of tumor immunology by tumor-secreted metabolites.

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Introduction

Tumor cells have an extraordinarily elevated requirement for nutrients to sustain their demanding anabolic needs and energy production rates. Thus, extracellular nutrients dictate the rate at which tumor cells proliferate. However, unlike normal cells, cancer cells have greater metabolic plasticity, which allows them to better adapt to lower or changing nutrient conditions [1] in ways that can, in turn, reshape the TME.

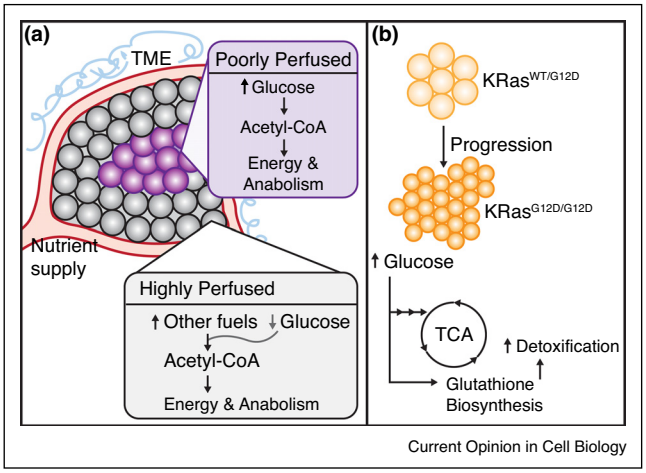
The TME (the non-cancerous components in close proximity to tumor tissue) has recently become the focus of intense research because of its clear role in the establishment and progression of cancer [2]. Thus, understanding the regulatory mechanisms that influence the TME could reveal novel avenues for cancer treatment. In solid tumors, the cancer microenvironment has two main components, cellular and non-cellular, whose proportion and composition vary depending on the tumor location and stage. The cellular components include fibroblasts, mesenchymal stem cells, adipocytes, pericytes, endothelial cells from the mesenchymal lineage, and tumor-infiltrating lymphocytes (TIL) and tumor-resident macrophages (TRM) from the lymphoid and myeloid lineages respectively [3]. Non-cellular components include mainly the extracellular matrix (ECM), which is composed of proteins, glycoproteins, and proteoglycans that act as a scaffold and maintain the tissue architecture [2].

In this review, we will summarize recent key discoveries that add to our understanding of tumor metabolism and how it affects the composition of the two main cellular constituents of the TME: fibroblasts and immune cells.

Tumor metabolic heterogeneity

One of the most striking characteristics of cancer cells is their ability to adapt to changing environmental conditions by utilizing a wide range of nutrients [4]. This is usually dictated by the supply of oxygen and nutrients delivered to the TME by the tumor vasculature [5], which is often not uniformly distributed across the tumor bulk. In this regard, a new study from Hensley *et al.* found that non-small cell lung cancers (NSCLC) exhibit heterogeneous intratumoral substrate utilization caused by variations in tissue perfusion [6••]. By using intraoperative 13C-glucose infusion in NSCLC patients [7], the authors found that tumor regions closer to well-vascularized areas, like normal lung tissue, were able to utilize fuels other than glucose to sustain growth, while less perfused regions used glucose as the main carbon source [6••] (Figure 1a). Importantly, the authors corroborated their model in two different NSCLC oncogenotypes, mutant EGFR and KRAS. Because oncogenes can modulate tumor metabolism [8,9], it still remains to be fully determined if other oncogenic drivers, other tissues of origin, or a more complex oncogenic composition in the tumor bulk [10,11] can also regionally influence substrate utilization. Supporting this concept, Kerr *et al.* recently showed that the acquisition of additional mutant $KRas^{G12D}$ alleles was linked to more advanced NSCLC in mice [12••]. Specifically, the authors showed that homozygous mutant $KRas^{G12D}$ cells had increased flux of glucose-derived carbon into the TCA cycle and glutathione biosynthesis, as compared to heterozygous counterparts. Ultimately, the gain in mutant allelic content allowed them to strengthen their glutathione-mediated detoxification [12••] (Figure 1b). This study provided the first in vivo

Figure 1



Tumor Metabolic Heterogeneity.
(a) Differential tumor vasculature perfusion promotes different carbon source usage in NSCLC. Low perfused areas use mainly glucose while highly perfused areas use other sources. **(b)** Oncogenic $KRas^{G12D}$ mutation load dictates a metabolic switch to an increased TCA-supported metabolism and augmented glutathione biosynthesis that increases the ROS-detoxifying ability.

evidence of how mutagenic load directly affects tumor metabolism and promotes tumor progression. Given that additional mutant $KRas^{G12D}$ are acquired during tumor progression, there is a point in time where homozygous and heterozygous $KRas^{G12D}$-containing cells with different metabolic activities coexist in the tumor bulk. This suggests that intratumoral mutational differences might, in addition to differential tissue perfusion, also contribute to a tumor's metabolic heterogeneity [6••].

Reprogrammed CAFs and stellate cells sustain tumor growth

CAFs make up a key stromal component that plays a fundamental role in tumor initiation, growth, invasion, and dissemination [13]. While normal fibroblasts (NF) undergo a reversible process of activation upon acute injury, known as the wound healing response [14], CAFs are chronically activated by environmental cues, mostly derived from the tumor's activity. Activated CAFs (also termed myofibroblasts) differ phenotypically from activated NFs in several ways including lower contractility, increased survival potential, increased proliferation, and augmented ECM remodeling ability [14].

Metabolic reprogramming is an emerging hallmark of CAF activation. Although more commonly attributed to tumor cells [15], a growing body of evidence shows that CAFs also undergo radical changes in their metabolism during activation. For instance, CAFs use aerobic glycolysis to sustain their augmented proliferation activity instead of relying on oxidative phosphorylation (OXPHOS) [16]. Their metabolism is also characterized by an increase in autophagy [17–19,20•] as a mechanism to mobilize internal sources of nutrients to provide the TCA with metabolic intermediates. A new study from Sousa *et al.* has provided a novel link between a myofibroblast-like cell, pancreatic stellate cells (PSCs), and tumor behavior. They showed that activated PSCs, in the context of pancreatic ductal adenocarcinoma (PDAC), secrete autophagy-derived alanine to sustain tumor metabolism [21••]. They also found that PSC-supplied free alanine could supplant glucose-derived carbon in TCA-cycle metabolites while diverting glucose utilization towards the serine and glycine one-carbon (SGOC) pathway, which functions in the *de-novo* synthesis of nucleotides [22] (Figure 2). This newly described mechanism could contribute to the resistance to nutrient stress observed in PDAC tumors by relieving the dependence on glucose and other nutrients. Similarly, Yang *et al.* recently reported that, under glutamine scarcity such as that observed in core regions of ovarian tumors, tumor-engaged CAFs harnessed carbon from diverse sources to produce glutamine for tumor cells [23]. Importantly, branched-chain amino acids (BCAA) and aspartate were the major substrates contributing to the nitrogen supply for glutamine synthesis in ovarian CAFs. Ultimately, the authors showed that combining simultaneous tumor and stromal targeting of glutamine usage pathways could efficiently prevent tumor growth in a mouse model of ovarian cancer [23••] (Figure 2). Both studies, Sousa *et al.* [21••] and Yang *et al.* [23], reported new tumor-feeding strategies of activated PSC and CAFs, respectively, which add to our understanding of TME crosstalk and offer potentially actionable targets. However, it is worth noting that PSC and ovarian CAFS rely on different mechanisms to mobilize amino acids (Figure 2). The specific signaling cascades that dictate which mechanism is used by CAFs and PSC to meet the nutritional demands of the tumor are not known. Additionally, since other tumor-feeding strategies have been discovered, such as exosome-mediated delivery of amino acids and TCA intermediates [24], it is yet to be determined whether there are tumor-derived cues that engage CAFs to deliver a specific nutrient or input back to the tumor. In this regard, recent work by Tape et al. [25] reported that a particular oncogene in tumor epithelial cells was able to induce CAF-dependent signaling. Specifically, they showed that $KRas^{G12D}$ was able to affect additional signaling pathways in tumor cells by non-cell autonomously engaging local heterotypic fibroblasts through SMO/Gli activity to signal back to tumor cells through an IGF1R/AXL-Akt-dependent axis. In this way, distinct metabolic, proliferative, anti-apoptotic, and anchorage-independent growth phenotypes in tumor cells would only be activated when tumor cells are in the presence of CAFs [25] (Figure 2). Taken together, these results suggest that there are, indeed, specific signaling mechanisms in the tumor that can hijack stromal components to