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The role of stroma in cancer metabolism

Alec C. Kimmelman[1,2,#], **Mara H. Sherman**[3,#]

[1]Perlmutter Cancer Center, New York University Grossman School of Medicine, New York, NY, USA.

[2]Department of Radiation Oncology, New York University Grossman School of Medicine, New York, NY, USA.

[3]Cancer Biology & Genetics Program, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

The altered metabolism of tumor cells is a well-known hallmark of cancer and is driven by multiple factors such as mutations in oncogenes and tumor suppressor genes, the origin of the tissue where the tumor arises, and the microenvironment of the tumor. These metabolic changes support the growth of cancer cells by providing energy and the necessary building blocks to sustain proliferation. Targeting these metabolic alterations therapeutically is a potential strategy to treat cancer, but it is challenging due to the metabolic plasticity of tumors. Cancer cells have developed ways to scavenge nutrients through autophagy and macropinocytosis and can also form metabolic networks with stromal cells in the tumor microenvironment. Understanding the role of the tumor microenvironment in tumor metabolism is crucial for effective therapeutic targeting. This chapter will discuss tumor metabolism and the contribution of the stroma in supporting tumor growth through metabolic interactions.

I. Introduction

It is well established that altered tumor cell metabolism is a hallmark of cellular transformation and a characteristic of the malignant state (Hanahan 2022). These changes are driven by a combination of factors including the mutational spectrum of the tumor (including oncogenes and tumor suppressor genes), the tissue of origin of the tumor, and the tumor microenvironment (DeBerardinis and Chandel 2016). Such metabolic alterations serve to support the unconstrained growth of cancer cells, providing the bioenergetic and anabolic needs for the developing tumor (Zhu and Thompson 2019). Causal roles for these metabolic alterations in tumor progression have motivated extensive effort to target these metabolic changes therapeutically as they represent potential therapeutic vulnerabilities. While some of these have shown promise and have moved forward into the clinic with

[#]To whom correspondence should be addressed: shermam1@mskcc.org, alec.kimmelman@nyulangone.org.

Disclosure of Potential Conflicts of Interest

A.C.K. has financial interests in Vescor Therapeutics and is an inventor on patents pertaining to KRAS- regulated metabolic pathways and redox control pathways in pancreatic cancer, targeting GOT1 as a therapeutic approach, targeting alanine transport, and the autophagic control of iron metabolism. A.C.K. is on the scientific advisory board of Rafael/Cornerstone Pharmaceuticals, OcoRev and has been a consultant for Deciphera and Abbvie. The other author declares no competing interests.

mixed results (Luengo et al. 2017), a common theme is that there is metabolic plasticity of tumors that is difficult to overcome (Biancur and Kimmelman 2018). Indeed, inhibition of single metabolic pathways in various tumor models often results in rapid metabolic rewiring to bypass the inhibited pathway (Biancur et al. 2017). Additionally, cancer cells have developed various mechanisms of "metabolic scavenging". These include catabolic processes such as autophagy and macropinocytosis whereby intracellular (autophagy) and extracellular (macropinocytosis) cargo are degraded by the lysosome and the resultant degraded products can fuel cellular metabolism (Encarnacion-Rosado and Kimmelman 2021). Tumor cells can also form heterocellular metabolic networks with stromal cells in the tumor microenvironment (TME) that can support various aspects of cancer growth (Lyssiotis and Kimmelman 2017). This chapter will discuss tumor metabolism with a particular focus on the various roles of the stroma in supporting tumor growth through metabolic contributions. We contend that to effectively target metabolism in the cancer cells themselves, one must also understand the contributions of the TME to these processes.

II. Metabolic features of non-malignant cell types in the tumor stroma

IIa. Metabolic milieu of the TME is a critical determinant of tumor biology

During tumorigenesis, the evolution of a unique TME imparts a set of selection pressures on the epithelial tumor cells that influences the fundamental biology of the cancer. The TME consists of a multitude of cell types, including fibroblasts, immune cells, neurons, and an abundant stromal matrix. The specific composition of TME cellular and acellular components are determined in part by the mutational landscape of the developing tumor, and reflect a perturbed wound-healing response. Recruitment, activation, and expansion of these TME components can lead to heterogeneous alterations in tissue oxygen (hypoxia) and nutrient content depending on stromal contexture, with profound consequences for the metabolic state of the tumor. The metabolic composition of the TME has gained attention in the recent years and a great deal of effort has gone into trying to assess the altered nutrient levels in various tumor types. Among solid tumors, pancreatic ductal adenocarcinoma (PDA) has particularly complex and abundant stroma, and is poorly perfused and extremely hypoxic (Halbrook et al. 2023). Because of this, there have been substantial efforts to understand the nutrient content of its TME and the impact of this on its metabolic dependencies. Based on the seminal findings that PDA can use extracellular protein to fuel metabolism via a process of bulk uptake and lysosomal degradation, termed macropinocytosis (Commisso et al. 2013), several groups have attempted to compare the nutrient content of freshly resected human PDA tumors compared to the adjacent normal pancreas (Kamphorst et al. 2015). This work demonstrated that tumors had reduced levels of glucose (including upper glycolytic intermediates), glutamine, and serine. It was also noted that amino acids used primarily for protein synthesis were enriched, which was consistent with increased protein scavenging via macropinocytosis. In an attempt to further refine the PDA nutrient content, Sullivan and colleagues performed metabolomics on tumor interstitial fluid (TIF) from mouse PDA models, as well as lung cancer models (Sullivan et al. 2019a). Interestingly, they showed that the nutrient content differed between lung and PDA, even when driven by the same oncogenic driver and tumor suppressor gene loss. Factors such as tumor location, type of tumors cells, and diet also influenced TIF metabolite

concentrations. Other groups have confirmed the altered nutrient content is affected by diet in head and neck cancer patients (Schroeder et al. 2013). Similar microdialysis studies in high grade astrocytoma patients showed decreased glucose in tumor compared to adjacent tissue (Roslin et al. 2003).

In addition to defining the altered nutrient content of the TME, several groups have explored how these nutrient differences impact aspects of tumor metabolism and biology. Using experimental models, Sullivan et al., showed that expression of PHGDH, the first rate limiting step of serine biosynthesis, benefits tumors specifically in tissues where serine is limited (Sullivan et al. 2019b). The Pacold and Cantley labs demonstrated that the ability of tumor cells to metastasize to the brain, an environment where serine is present at low levels, requires intact an intact serine synthesis pathway (Ngo et al. 2020). Indeed, inhibition of PHGDH selectively attenuated brain metastasis growth, while extracranial growth was largely unaffected. Similarly, Ferraro et al. show that the brain is low in lipid availability and this causes breast cancer cells that metastasize to the brain to upregulate fatty acid synthesis (Ferraro et al. 2021). Given the impact of the nutrient content of the TME on the tumor, there are significant efforts to utilize this information for the purposes of understanding the metabolic dependencies of cancer cells. These include developing modified media formulations to better reflect the metabolic content of the TME and enable more meaningful cell culture studies (Cantor et al. 2017), as well as performing functional genomic screens in the in vivo setting where cells are in the appropriate TME (Biancur et al. 2021; Zhu et al. 2021). Both approaches have yielded potential novel metabolic targets, but more work is needed in these areas.

As mentioned previously, there are a multitude of cell types within the TME, making it likely that a competition for nutrient availability exists. Indeed, several groups have demonstrated that infiltrating immune cells compete with tumor cells for critical nutrients. The Pearce and Kaech groups showed that there is intense competition between tumor infiltrating T cells and the highly glycolytic tumor cells in sarcoma and melanoma models respectively (Chang et al. 2015; Ho et al. 2015). Limiting glucose to the effector T cells can impair their function and dampen anti-tumor immunity. Treatment with anti-PD-L1 blocking antibodies can decrease tumor cell glycolytic activity, improve T cell access to glucose, and enhance T cell activation. Alternatively, T cells can upregulate phosphoenolpyruvate (PEP) production (a glycolytic intermediate) through overexpression of phosphoenolpyruvate carboxykinase 1 (PCK1) which leads to improved anti-tumor functions. Similarly, it was shown that the hypoxic and glucose deprived melanoma TME causes an increased utilization of fatty acids by the effector T cells, thereby improving their anti-tumor response. Reinfeld and colleagues used PET tracers to show that there was preferential uptake of glutamine by the tumor cells, with myeloid cells and T cells showing the highest avidity for glucose (Reinfeld et al. 2021). Interestingly, they demonstrated that this nutrient partitioning was cell intrinsic and not due to glucose being limiting in the TME. Thus it appears, that there are multiple mechanisms that govern nutrient competition in the TME that can include limiting concentrations in the tumor or cell intrinsic properties of particular cell types. Understanding these factors, will be critical to optimize therapeutic efficacy.

IIb. Metabolic features and consequences of the tumor vasculature

Solid tumors require a vascular supply to enable progression. Sufficient vascularization results from one of two general mechanisms: induction of angiogenesis or the formation of new blood vessels by reprogramming of quiescent endothelial cells, known as the angiogenic switch; or vessel co-option, whereby cancer cells migrate along or infiltrate between pre-existing vessels in benign tumor-adjacent tissue, ultimately leading to the incorporation of these vessels into the tumor (Kuczynski et al. 2019; Hanahan 2022). This requirement reflects the dependence of cancer cells on oxygen and nutrients delivered by the circulatory system, such that tumor-associated vasculature provides critical metabolic inputs once the limits of oxygen diffusion are exceeded. This need for the vasculature to provide metabolites is overcome to some extent by metabolic reprogramming of other non-malignant cell types in the tumor microenvironment, discussed in detail in the sections below. However, the association between microvessel density and tumor grade in multiple tumor types (Weidner et al. 1991; Macchiarini et al. 1992; Weidner et al. 1993; Benckert et al. 2012) as well as the pervasive use of hematogenous or lymphatic dissemination as a route of metastasis (Lambert et al. 2017; Follain et al. 2020; Reticker-Flynn et al. 2022) underscore the significance of endothelial cells in cancer. While the mechanisms underlying vessel co-option remain poorly understood, tumor angiogenesis is known to require extensive metabolic adaptation among endothelial cells (Zecchin et al. 2017). Quiescent endothelial cells switch to migratory tip cell or proliferative stalk cell fates and sprout into poorly vascularized tissues including hypoxic tumors to form new blood vessels during angiogenesis, a process featuring activation of glycolysis in both migratory tip cells and proliferative stalk cells by 6-phosphofructo-2-kinase/fructose-2,6-bisphosphate 3 (PFKFB3) (De Bock et al. 2013; Li et al. 2019). Tracing studies of tumor endothelial cells in culture using ^{14}C-glucose and ^{13}C-glucose showed use of glucose carbons for nucleotide synthesis (Cantelmo et al. 2016), linking the hyperglycolytic metabolism of tumor endothelial cells to biomass production. Loss of a single allele of *Pfkfb3* in endothelial cells did not impact tumor size, but reduced cancer cell intravasation and metastasis together with reduced vessel tortuosity and improved perfusion dynamics (Cantelmo et al. 2016). These structural features of a normalized vasculature are typically associated with intact adherens junctions and vascular barriers which limit cancer cell spread, suggesting endothelial cell metabolism as a potential target to normalize tumor vasculature and limit metastasis.

Blood vessels in tumors are structurally abnormal or tortuous and typically hyperpermeable, together causing fluid leakage, compromising blood perfusion, and exacerbating hypoxia and acidity (Jain 2005). Vessel dysfunction results in part from mechanical forces within the tumor stroma (Provenzano et al. 2012; Stylianopoulos et al. 2012), and necessitates adaptive mechanisms in the neoplastic compartment to maintain viability and proliferative capacity in the context of relatively low oxygen, serum nutrients, and pH. These adaptive mechanisms include hypoxia-driven enhancement of macropinocytosis to obtain amino acids and other nutrients from the extracellular space, mediated by hypoxia-inducible factor 1-alpha (HIF-1α) as well as mutant KRAS (Commisso et al. 2013; Garcia-Bermudez et al. 2022). Metabolic heterogeneity among poorly perfused versus relatively well perfused regions of human lung cancer have been reported, highlighting potentially limited nutrient availability in poorly perfused tissue areas reflected by increased contribution of glucose—as opposed to

other available metabolites—to the TCA cycle (Hensley et al. 2016). Important adaptations to tumor acidification include use of lactate as a carbon source (Faubert et al. 2017; Hui et al. 2017), while adaptations to low oxygen include increased uptake and use of unsaturated fatty acids which do not require oxygen-dependent desaturation (Ackerman and Simon 2014). While these and other adaptations to metabolic stress enable cancer cell proliferation and survival, they may also represent vulnerabilities for therapeutic intervention.

III. Stromal catabolic processes supporting cancer cell metabolic fitness

IIIa. Significance of stromal autophagy and macropinocytosis for cancer cell viability

While the importance of nutrient scavenging and catabolism in the tumor epithelium has been recognized for over a decade, the significance of these processes in the adjacent stroma has more recently come to light. In an effort to explore additional nutrient sources for pancreatic cancer cells, Sousa et al. identified a novel metabolic crosstalk between the cancer associated fibroblasts (CAFs) and the pancreatic cancer epithelial tumor cells (Sousa et al. 2016). The CAFs were secreting high levels of the amino acid alanine, which the tumor cells could use to fuel metabolic processes under nutrient limiting conditions. Interestingly, the secretion of alanine was dependent of the autophagy/lysosome system (Figure 1). Consistent with this, inhibition of autophagy in the CAFs decreased alanine secretion and impaired tumor take in co-injection studies. Other studies have also confirmed the importance of autophagy in the stroma in promoting pancreatic cancer growth (Endo et al. 2017). In a follow-up study, the nutrient transporter required for alanine uptake in pancreatic cancer cells, SLC38A2, was identified. SLC38A2 was shown to be critical for metabolic homeostasis in these cells and was required for tumor growth (Parker et al. 2020). In a related manner, Zhang et al. demonstrated that pancreatic CAFs utilize macropinocytosis under nutrient limited conditions to support their own metabolism, but also to allow the secretion of amino acids to fuel the metabolism of pancreatic cancer cells (Zhang et al. 2021). Studies in prostate cancer showed similar findings, whereby Ras activity is upregulated in prostate CAFs through the epigenetic silencing of a negative Ras regulator (Mishra et al. 2018). This increases macropinocytosis and allows the CAFs to supply glutamine to the cancer cells to fuel metabolic processes, but also promotes neuroendocrine differentiation.

IIIb. Paracrine regulation of lipid metabolism

Co-option of non-malignant cell types in the tumor microenvironment for metabolic support extends to cancer-associated adipocytes in several tissue contexts where tumors or metastases grow in the vicinity of adipose tissue. Multiple tumor types including prostate, breast, lung, colon, and ovarian cancer; melanoma; and hematologic malignancies, stimulate lipolysis in nearby adipocytes and take up adipocyte-derived fatty acids to support tumor growth and metastasis (Mukherjee et al. 2022). For example, advanced melanoma grows past the dermis into adipocyte-rich subcutaneous tissue, with the potential to metastasize to secondary subcutaneous tissues. Melanoma cells have long been known to harbor lipolytic activity (Hollander et al. 1986), and a recent study demonstrated that adipocytes increase melanoma cell proliferation and invasion (Zhang et al. 2018). Melanoma cells stimulate fatty acid release by adipocytes, which are in turn taken up by melanoma cells in part via FATP1

to contribute to melanoma cell lipid pools. Inhibition of FATP proteins with small molecule inhibitor Lipofermata blocked lipid transfer into melanoma cells, and this suppression of adipocyte-melanoma crosstalk reduced paracrine induction of proliferation and invasion. The mechanistic links between fatty acid uptake and cancer cell invasiveness remain unclear and warrant further investigation. Functional, bi-directional interactions between adipocytes and cancer cells were also reported in ovarian cancer, which frequently metastasizes to the adipocyte-rich omentum. Ovarian cancer cells induce lipolysis in adipocytes, which in turn provide lipids to cancer cells, induce β-oxidation, and promote tumor growth (Nieman et al. 2011). The tumor-promoting effects of adipocytes were also mediated by adipokines including IL-8, which promote ovarian cancer cell homing, migration, and invasion in the omentum. Adipocytes were later shown to induce expression of lipid chaperone protein FABP4 in ovarian cancer cells, which critically regulates adipocyte-driven alterations to ovarian cancer cell lipid metabolism and ultimately supports both tumor growth and, somewhat surprisingly, resistance to chemotherapeutic agent carboplatin (Mukherjee et al. 2020). Additional mechanisms by which stromal metabolism promotes chemoresistance are discussed in the next section.

Breast cancer is somewhat unique in that primary breast tumors develop within the adipose-dominated mammary tumor microenvironment. Recent transcriptomic analysis of both breast cancer cells and adjacent mammary adipose tissue identified critical roles for glycine amidinotransferase (GATM) in adipocytes and acyl-CoA synthetase bubblegum family member 1 (ACSBG1) in cancer cells for breast tumor progression (Maguire et al. 2021). Linking these pathways is creatine, which is released by adipocytes and taken up by breast cancer cells to promote proliferation. Breast cancer-associated adipocytes also express extracellular matrix remodelling enzymes such as MMP-11 and pro-inflammatory cytokines such as IL-6 and IL-1β, together supporting breast cancer cell invasiveness (Dirat et al. 2011). Further highlighting the metastasis-promoting potential of local adipose tissue, expression of the fatty acid translocase CD36, a transmembrane glycoprotein receptor with a high affinity for long-chain fatty acids, is high on metastasis-initiating cells and associates with a poor prognosis among breast cancer patients (Pascual et al. 2017). These tumor-promoting functions of local adipose tissue and adipose-derived fatty acids may explain in part the epidemiologic evidence supporting an association of obesity with breast cancer (Lauby-Secretan et al. 2016).

IIIc. Stromal supply of nucleic and branched-chain amino acids to cancer cells

Tumor cells stimulate catabolic processes in surrounding stromal cells beyond lipolysis and autophagy as described above, which make distinct contributions to tumor cell metabolic fitness. One such process was recently demonstrated in the context of pancreatic cancer. PDA cells take up and use glutamine as a TCA carbon source (Son et al. 2013), such that environmental glutamine levels in the PDA microenvironment are low compared to benign pancreas tissue (Kamphorst et al. 2015; Lee et al. 2019). A recent study demonstrated that conditions of low glutamine stimulate the accumulation of nuclear fragile X mental retardation-interacting protein 1 (NUFIP1) in the cytoplasm of pancreatic cancer-associated fibroblasts (CAFs), where NUFIP1 degrades ribosomal RNAs (rRNAs) (Yuan et al. 2022). These NUFIP1-generated nucleosides are then secreted and taken up by PDA cells, resulting

in stabilization of oncogenic transcription factor MYC, elevated expression of MYC target SLC2A1, and increased glucose uptake to promote tumor growth. While CAFs provide secreted factors which enable PDA cell proliferation under low-glutamine conditions, loss of NUFIP1 expression by CAFs abolished this effect. CAFs also support PDA cell proliferation by providing substrates for *de novo* protein synthesis (Zhu et al. 2020). CAFs express high levels of branched-chain amino acid transaminase 1 (BCAT1), far exceeding BCAT1 expression in tumor cells. BCAT1 induction in CAFs results from TGF-β signaling, originating from cancer cells and perhaps additional cellular sources, via SMAD5. Stromal BCAT1 in turn catabolizes extracellular matrix proteins and potentially other substrates to generate branched-chain ketoacids, which are taken up by PDA cells and used for protein synthesis. In addition to supporting proliferation under conditions of nutrient challenge, CAFs also support PDA cell resistance to chemotherapy and viability in the context of gemcitabine treatment. PDA CAFs secrete sufficiently high levels of deoxycytidine, through equilibrative nucleoside transporters, to inhibit the processing and cytotoxic activity of gemcitabine in PDA cells (Dalin et al. 2019). Tumor-associated macrophages in PDA were similarly shown to secrete deoxycytidine and promote gemcitabine resistance (Halbrook et al. 2019), further linking stromal metabolism to therapeutic resistance.

IIId. Role of p62 in the stroma for metabolic reprogramming and tumor progression

P62 (SQSTM1) is a multifunctional signaling hub that has been most well studied as an autophagy adaptor (Moscat and Diaz-Meco 2011). Interestingly, while p62 upregulation in the tumor epithelium has been shown in several cancers to be oncogenic in nature (Reina-Campos et al. 2018), its loss in the stroma of certain tumor types has been shown to support cancer growth through a number of mechanisms including altering cellular metabolism. In prostate cancer CAFs, loss of P62 causes a series of metabolic effects that ultimately supports prostate cancer growth. For example, in a low glutamine environment, CAFs lacking p62 increase expression of asparagine synthetase (ASNS) which leads to increased secretion of asparagine. This asparagine can be utilized by the tumor cells as a fuel source. These CAFs also upregulate pyruvate carboxylase (PC) that can help compensate for decreased α-ketoglutarate from a low glutamine environment and allow the CAFs to thrive. Consistent with the importance of stromal P62 in supporting tumor growth, knockout of P62 in fibroblasts induced premalignant prostate lesions (Valencia et al. 2014). Loss of p62 expression in adjacent fibroblasts is driven by malignant epithelial cells via secreted lactate, which suppresses activity of AP-1 transcription factors in CAFs leading to transcriptional downregulation of *Sqstm1* (encoding p62) (Linares et al. 2022). Tumor-restraining potential of stromal p62 extends to adipose tissue as well, where p62 loss results in osteopontin release from adipocytes and consequent increases in cancer cell CPT1 expression, fatty acid oxidation, and tumor progression (Huang et al. 2018). While these context-dependent roles for p62 have mostly been studied in prostate cancer, these roles may extend to other tumor types, and opposing roles of metabolic signaling hubs in tumor cells versus surrounding stroma may also be more broadly relevant.

IV. Paracrine regulation of cancer cell metabolic signaling networks

IVa. Activation of mitogenic and metabolic signaling nodes by stromal cues

The studies discussed above provide evidence that stromal cells secrete metabolites through diverse mechanisms that can be taken up by cancer cells to contribute to their metabolite pools and reduce the need for *de novo* synthesis reactions. However, these stroma-derived metabolites also serve as functional mediators of paracrine signaling, which can further impact cancer cell-intrinsic metabolic processes via metabolite-responsive signaling pathways (Figure 2). This basis for coupling of stromal and epithelial metabolic processes was recently demonstrated in PDA. Normal pancreas tissue harbors a population of tissue-resident mesenchymal cells called stellate cells, which regulate tissue homeostasis including baseline production and recycling of extracellular matrix and basement membrane components (Sherman 2018). Pancreatic stellate cells (PSCs) are characterized in part by abundant, cytoplasmic lipid droplets which store vitamin A as retinyl esters and give PSCs a blue-green autofluorescence that facilitates visualization and analysis. In the context of tissue damage or during pancreatic tumorigenesis, PSCs become activated, and differentiate from their quiescent state to a myofibroblastic phenotype. In the activation process, PSCs lose their lipid droplets and downregulate a transcriptional program associated with lipid storage, coincident with upregulation of genes associated with CAF functions (Sherman et al. 2014). As this stromal lipid metabolic switch accompanies pancreatic tumor progression, lipidomic analyses of PSC-intrinsic and secreted lipid species were performed and revealed that PSCs undergo extensive lipidomic remodeling upon activation (Auciello et al. 2019). Activated PSC secrete abundant lysophosphatidylcholines (LPCs), the preferred fatty acid scavenging substrate for RAS-transformed cells including PDA cells (Kamphorst et al. 2013). In addition to their utility for uptake and nutrient scavenging, though, LPCs can also regulate cancer cell metabolism via signaling. LPCs are hydrolyzed by the secreted enzyme autotaxin, with lysophospholipase D activity, to yield lysophosphatidic acid (LPA) species (Perrakis and Moolenaar 2014). PDA cells express and secrete high levels of autotaxin, which hydroyzes stroma-derived LPC to yield LPA in the pancreatic tumor microenvironment (Auciello et al. 2019). LPA in turn signals through G-protein-coupled LPA receptors (LPARs) on PDA cells to activate mitogenic signaling pathways including the PI-3 kinase/AKT pathway, significant in the context of PDA as PI-3K mutations are exceedingly rare in this disease setting. Genetic or pharmacologic inhibition of autotaxin reduces both AKT activation and PDA growth *in vivo*, and may also impact additional metabolic signaling pathways downstream of LPARs (Mills and Moolenaar 2003).

An unexpected signaling mechanism was recently shown to co-regulate AKT signaling in both tumor cells and stromal cells. Compared to normal tissue fibroblasts, CAFs express high levels of presynaptic protein Netrin G1 (NetG1), which signals through NetG1 ligand 1 (NGL1) or NGL1-independent mechanisms on neighboring cells (Francescone et al. 2021). NetG1 expression on CAFs positively regulates AKT activation in a cell-intrinsic manner, but also activates AKT in PDA cells in a paracrine manner mediated by NetG1-dependent small extracellular vesicle production (Raghavan et al. 2022). Stromal NetG1 and consequent paracrine activation of AKT helps PDA cells survive under relevant conditions of nutrient challenge. NetG1 on CAFs further regulates PDA cell metabolism by interacting

with NGL1 on the PDA cell surface and inducing macropinocytosis, though the precise signaling pathway linking NetG1-NGL1 engagement to induction of macropinocytosis remain to be determined. The relevance of stromal NetG1 for cancer cell metabolic signaling in other tumor settings has not been assessed and warrants investigation.

IVb. Neuron-derived serine in cancer cell mRNA translation

Pancreatic cancers are amongst the most highly innervated of human tumors which can lead to an intractable pain syndrome in patients (Lohse and Brothers 2020). While it has been well known that neurons can support the growth of cancers, including pancreatic cancer, most of this work has focused on the secretion of growth factors by the neurons that are used by the cancer cells (Renz et al. 2018). Recently, it was shown that nerves also play a critical metabolic role in pancreatic tumors through the secretion of metabolites (Banh et al. 2020). Conceptually, neurons are ideally suited to be a nutritional conduit to the nutrient deprived areas of tumor. While the axons are in the TME, the cell body is actually in the ganglion, bathed by the nutrient rich systemic circulation. Using a microfluidic chamber, Banh et al. showed that rat dorsal root ganglion neurons were capable of secreting amino acids from their axons (Banh et al. 2020). They went on to show that neuronal secretion of serine and glycine could support the growth of a large subset of pancreatic cancer cells that are unable to biosynthesize serine due to loss of PHGDH. Interestingly, they identified that the cancer cells required serine and glycine for proper RNA translation and that pancreatic cancer cells deficient in serine synthesis showed differential translation of particular serine codons, resulting in an adaptive biological program that slows proliferation, but increased secretion of Nerve Growth Factor (NGF). Thus, serine deprivation resulted in increased innervation of the pancreatic tumors to support tumor growth by providing serine. Combining a serine/glycine free diet with an NGF receptor inhibitor significantly decreased the growth of serine-dependent pancreatic cancer cells. Further efforts are underway to determine if this biological adaptation can be exploited for therapeutic purposes and warrant investigation in other tumor types featuring peripheral innervation.

IVc. Crosstalk between fibroblasts and cancer cells to support oncogene signaling

Examples of stroma-derived metabolites supporting cancer cell proliferation and survival call into question how stromal cells can bioenergetically “afford” to spare metabolites for the purpose of cancer cell fitness, as these stromal cells (with the exception of nerves, as described above) reside in the same inhospitable microenvironment as the tumor cells they functionally feed. These interactions may reflect an evolutionarily conserved relationship for stromal cells in the context of wound healing reactions, where professional fibro-inflammatory cells secrete diverse factors to enable epithelial cell proliferation and tissue repair. Stromal cell proliferation rates are lower than those of regenerating epithelium in wounds, and lower than cancer cells in tumors, consistent with co-evolution of epithelial and stromal compartments such that stromal cells secrete metabolites than help tumor cells proliferate and survive. Even with a relatively low proliferation rate to limit biomass demand among stromal cells, these cells must adapt to their surroundings in the context of a tumor to produce and secrete molecules that facilitate growth in a paracrine manner. An important adaptation enabling metabolic crosstalk between stromal and cancer cells was identified by comparing normal ovarian fibroblasts to ovarian CAFs (Yang et al. 2016).

Transcriptional profiling of high-grade serous ovarian CAFs compared to normal fibroblasts revealed strikingly higher expression of genes involved in glutamine anabolic pathways in CAFs. Further, CAFs had far greater metabolic flexibility than normal fibroblasts, including adaptive mechanisms for harnessing carbon and nitrogen from atypical sources to enable glutamine synthesis in environments where glutamine is scarce. High expression of glutamine synthetase by CAFs was crucial for efficient stromal glutamine production, and combined inhibition of stromal glutamine synthetase and glutaminase within tumor cells served as a synthetic lethal approach leading to reduced tumor growth and metastasis. In-depth analyses of co-evolving metabolic adaptations in tumor and stroma may point to additional avenues for combined targeting to suppress tumor progression.

While cancer cells undergo cell-intrinsic metabolic reprogramming over the course of tumor initiation and progression mediated by core oncogenic signaling pathways, stromal components further influence cancer cell metabolism by cooperatively activating oncogenic signaling nodes to augment metabolic transcriptional outputs. In the pancreas, oncogenic KRAS and its gene-regulatory effector MYC drive an anabolic transcriptional program including components of the hexosamine biosynthesis and pentose phosphate pathways (Ying et al. 2012). Despite pervasive regulation of oncogenic transcription by mutant KRAS and MYC, expression of KRAS G12D throughout the pancreatic epithelium is insufficient to drive tumorigenesis in adult mice (Guerra et al. 2007). A fibro-inflammatory reaction cooperated with oncogenic KRAS to promote pancreatic tumorigenesis, implicating this stromal reaction as a permissive context for tumor initiation and early progression. While inflammation limits barriers to tumor formation in place under homeostatic conditions, stromal cues also promote KRAS-driven tumorigenesis by cooperating with cancer cell-intrinsic KRAS signaling to promote expression of genes involved in metabolic reprogramming and immune suppression (Sherman et al. 2017; Alonso-Curbelo et al. 2021). Gene expression programs and many gene identities were co-regulated by KRAS and stromal cues, with highest expression of these genes in the context of both cell-intrinsic and microenvironmental inputs. These findings suggest gene-regulatory points of convergence for oncogenic and stromal signaling pathways that together enable metabolic reprogramming to support tumor growth.

V. Wound-healing mediators as metabolic regulators

The dense extracellular matrix associated with many solid tumors has long been implicated in mechanosignaling and tumor progression, but recently has been reported as a metabolic signaling mediator and a potential fuel source. Collagen is particularly abundant in solid tumor microenvironments, and dynamic matrix remodeling yields collagen fragments which may be taken up by cancer cells via macropinocytosis or other mechanisms (Olivares et al. 2017). As proline comprises 25% of the total amino acid composition of collagen, these collagen fragments serve as a proline reservoir which can promote cancer cell viability under nutrient-limited conditions. Collagen-derived proline contributes to PDA cell metabolism, and proline oxidase is required for PDA cell proliferation both *in vitro* and *in vivo* (Olivares et al. 2017). Proline oxidase is similarly needed to support colorectal cancer cell survival, yielding ATP in the setting of nutrient restriction and inducing autophagy under hypoxic conditions (Liu et al. 2012). Collagen is mostly produced by CAFs, and

the metabolic state of CAFs dictates their capacity for matrix production. The cystine transporter SLC7A11, previously implicated as a therapeutic target on PDA cells (Badgley et al. 2020), also promotes tumor growth through its functions in the stroma (Sharbeen et al. 2021). SLC7A11 promotes cystine uptake and glutathione synthesis by CAFs, and stromal SLC7A11 inhibition reduces CAF proliferation as well as their ability to produce and remodel collagen, and to support tumor growth. Pro-tumorigenic collagen production by CAFs also requires proline synthesis from glutamine by PYCR1 (Kay et al. 2022), such that PYCR1 inhibition in breast CAFs is sufficient to reduce collagen production, tumor growth, and metastatic spread. The master fibrogenic signaling mediator TGF-β promotes collagen production by CAFs, and was recently shown to support the bioenergetic cost of matrix protein synthesis in part by increasing mitochondrial oxidation of glucose and glutamine (Schworer et al. 2020). TGF-β signaling also stimulates proline biosynthesis from glutamine in a SMAD4-dependent manner. To reconcile collagen production with the glutamine- and glucose-low environments in which CAFs often function, a recent study demonstrated that pyruvate carboxylase-mediated anaplerosis within CAFs supports use of extracellular lactate to fuel the TCA cycle, non-essential amino acid biosynthesis, and collagen synthesis (Schworer et al. 2021). Like collagen, hyaluronic acid (HA) is an abundant component of tumor microenvironments, and can also be used as a fuel source. HA consists of repeating *N*-acetyl-glucosamine (GlcNAc) and glucuronic acid sugars, and can contribute to the hexosamine biosynthesis pathway via GlcNAc salvage (Kim et al. 2021). Consistent with these findings, GlcNAc salvage via *N*-acetylglucosamine kinase (NAGK) promotes protein glycosylation and tumor growth *in vivo* (Campbell et al. 2021). HA remodeling and fragmentation further impacts cancer cell metabolism by negatively regulating TXNIP, increasing GLUT1 abundance at the plasma membrane, and increasing glucose uptake and glycolysis (Sullivan et al. 2018). Together, these studies highlight the significance of the extracellular matrix for cancer metabolism, and in turn, the importance of fibroblast metabolism for matrix production in tumors.

In addition to matrix components, soluble mediators of wound-healing reactions have also been implicated in the regulation of cancer cell metabolism. As described above, cancer cell-intrinsic KRAS signaling cooperates with stromal cues to promote expression of an anabolic transcriptional program, including many MYC target genes. Mechanistically, CAFs secrete high levels of acidic fibroblast growth factor (FGF1), which signals to cancer cells in a paracrine manner to activate AKT, negatively regulate GSK-3β, and elevate MYC stability and expression in the context of mutant KRAS (Bhattacharyya et al. 2020). CAF-derived cytokines and chemokines may also indirectly impact cancer cell metabolism by regulating the abundance and phenotypes of tumor-infiltrating immune cells. CAF secretion of CXCL12/SDF1, M-CSF/CSF1, IL6, and CCL2/MCP1 can all contribute to the recruitment of tumor-associated macrophages as well as their Arginase-expressing, immunosuppressive phenotype (Sanford-Crane et al. 2019). Arginine-metabolizing myeloid cells create a growth permissive niche for lung cancer (Fu et al. 2022), neuroblastoma (Van de Velde et al. 2021), and other tumor types (Grzywa et al. 2020), perhaps reflecting the role of arginine metabolism in the resolution of tissue injury (Yurdagul et al. 2020).

VI. Targeting stromal metabolism for cancer therapy

While the wound-like microenvironments associated with many solid tumors permits or supports progression, these niches also establish growth requirements distinct from healthy tissue which may be targetable for therapeutic benefit. Targeting tumor cells as well as their niche may overcome cancer cell-intrinsic metabolic plasticity that has limited the efficacy of therapeutic agents targeting metabolic pathways. For example, Ras-transformed cancer cells as well as cancer cells under hypoxia take up lipids from the extracellular space and scavenge fatty acids from these lipids to limit the need for *de novo* lipid synthesis and oxygen-dependent desaturation reactions (Kamphorst et al. 2013). As stromal cells provide specific lipid species to tumor cells to support their proliferative capacity (Zhang et al. 2018; Auciello et al. 2019), particularly within poorly perfused contexts, combination therapies targeting stromal lipid metabolism as well as adaptation mechanisms in tumor cells may meaningfully limit cancer cell viability within an intact tumor microenvironment. Evidence in melanoma suggests that targeting stromal lipid metabolism may also foster the efficacy of targeted therapies (Alicea et al. 2020). Along a similar vein, recent work demonstrated the tumor-promoting roles for catabolic processes including autophagy and macropinocytosis in the stroma associated with cancer cells (Yang et al. 2018; Zhang et al. 2021). These findings in PDA complement recent work in lung cancer indicating the potential to foster anti-tumor immunity by inhibiting autophagy systemically (Poillet-Perez et al. 2020; Khayati et al. 2022), via cancer cell non-autonomous mechanisms that may include stromal cells in the tumor microenvironment as well as distant organs. These studies highlight the potential for inhibitors of these mechanisms to perturb stromal metabolic support to tumor cells, as well as growth-permissive crosstalk with the immune system. While the antitumor potential of autophagy inhibitor hydroxychloroquine is already under investigation in clinical trials in combination with cytotoxic chemotherapy (Zeh et al. 2020) and other agents, a deeper understanding of the consequences of stromal catabolic processes may point to new, rationally designed combination therapy studies.

VII. Conclusions and future directions

Over the course of this chapter, we have described diverse modes of tumor-stroma crosstalk that impact cancer cell metabolism and tumor progression. Some of these crosstalk mechanisms may reflect the metabolic reprogramming associated with productive wound healing reactions (Shyh-Chang et al. 2013), highjacked in the context of cancer. Others may be tumor-specific. Given the increasingly appreciated role of stromal metabolism in both tumor progression and therapeutic resistance, our evolving understanding of metabolic support functions in intact tumor microenvironments may point to critical pathways to target for combination therapy. While the heterogeneity and plasticity of tumor cells with respect to their metabolism creates a challenge for productive therapeutic targeting of metabolic pathways, further study of cancer metabolism in the proper tissue setting has the potential to identify contextual dependencies that may be exploited effectively. To this end, important goals of future investigation include a deeper understanding of intratumor metabolic heterogeneity as well as the mechanisms enabling metabolic plasticity. State-of-the-art metabolomic technologies increasingly enable analysis of metabolic processes within heterocellular tumor tissues (Nascentes Melo et al. 2022), and their continued development

will serve the field well in striving to understand relationships between tumor cell and stromal cell metabolism within relevant anatomic contexts.

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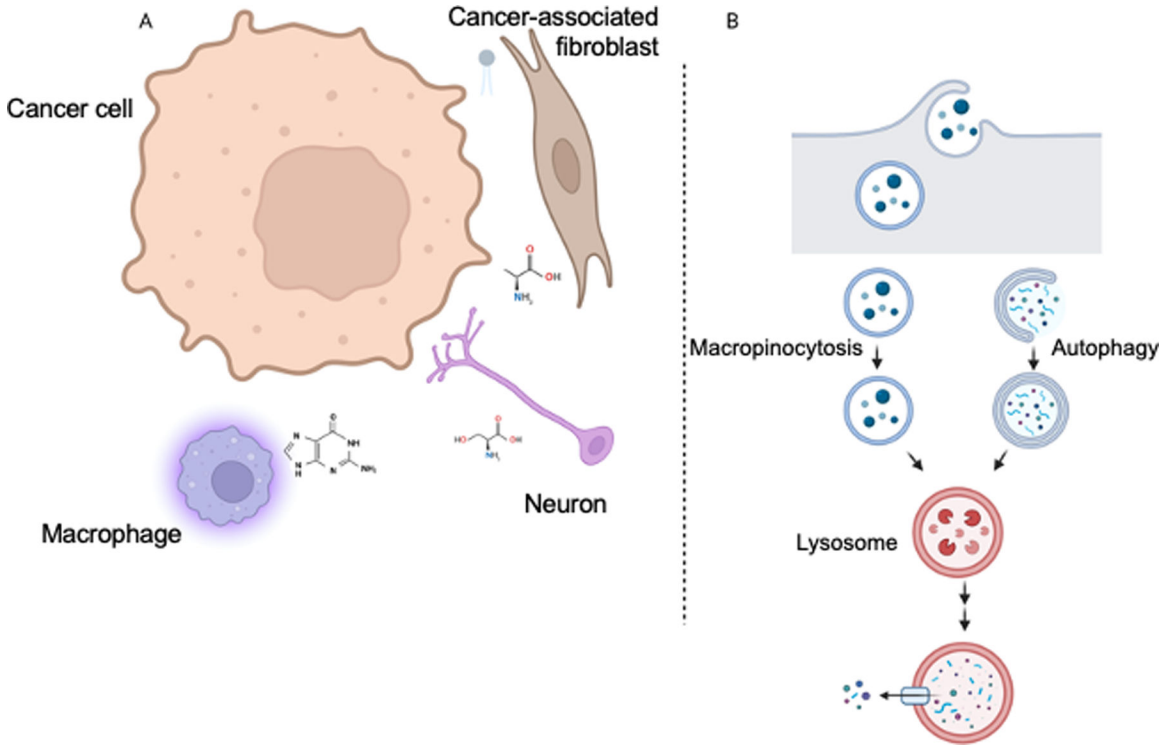

Figure 1.

(A) Cancer cells obtain nutrients from surrounding immune and non-immune stromal cells to support proliferation, viability, and resistance to therapy. This paracrine metabolic support includes alanine and specific lysolipid species from cancer-associated fibroblasts, which support mitochondrial metabolism and membrane synthesis respectively; serine from peripheral axons to regulate mRNA translation; and pyrimidines from macrophages, which promote resistance to standard of care chemotherapeutic agent gemcitabine. **(B)** Both cancer cells and non-transformed stromal cells take up nutrients from the extracellular space via macropinocytosis, and degrade intracellular cargo by autophagy. These processes converge at the lysosome, enabling recycling of nutrients which may be secreted and used by neighboring cells to support metabolic processes in a paracrine manner.

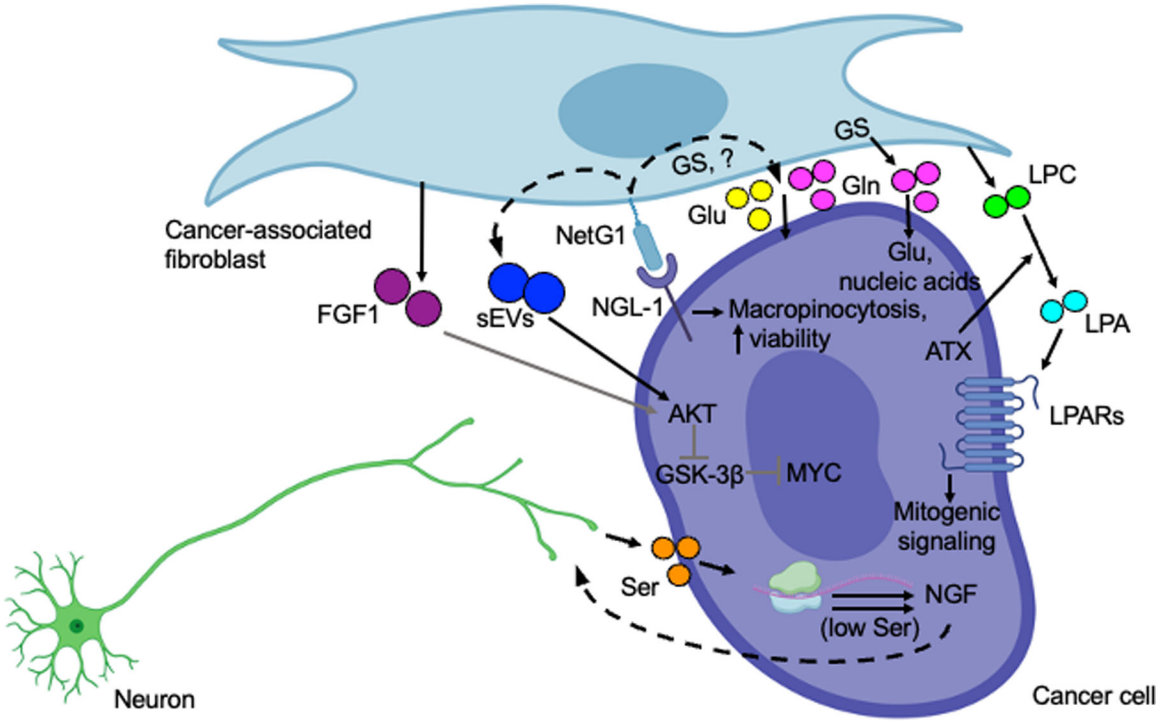

Figure 2.

Signaling mediators from stromal cells, including cancer-associated fibroblasts and neurons, regulate cancer cell metabolic and mitogenic pathways in a paracrine manner. GS: glutamine synthetase, Gln: glutamine, Glu: glutamate, sEVs: small extracellular vesicles, LPC: lysophosphatidylcholine, LPA: lysophosphatidic acid, ATX: autotaxin, NGF: nerve growth factor, Ser: serine, FGF1: acidic fibroblast growth factor.