How Tumor Microenvironment Alters Metabolism in Cancer Cells

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Abstract

Cancer cells usually reside in microenvironment stress, such as hypoxia, acidosis, Hypo-nutrition and Inflammation. In order to withstand the harsh microenvironment stress, cancer cells engage multiple evolutionarily conserved molecular responses to confer the ability to survive and proliferate. These responses to changes in microenvironment stress availability promote altered metabolism, called "metabolic reprogramming", which has been recognized as one of 10 hallmarks of cancer. Metabolic reprogramming is required for both malignant transformation and tumor development, including invasion and metastasis. Although the Warburg effect has been widely accepted as a common feature of metabolic reprogramming, accumulating evidence has revealed that tumor cells depend on mitochondrial metabolism as well as aerobic glycolysis. In addition, deregulated metabolism of glucose, glutamine and lipids under microenvironment stress have been identified to function as metabolic regulators in supporting cancer cell growth. Furthermore, extensive crosstalks are being revealed between the deregulated metabolic network and cancer cell signaling under microenvironment stress. These exciting advancements have inspired new novel strategies for treating various malignancies by targeting microenvironment factors. Here we review recent findings related to the regulation of microenvironment stress induced metabolic changes, and present future directions in this rapidly emerging area

Introduction

For many years, cancer studies and cancer-related research were focused only on cancer as being limited just to cancer cells, ignoring the environment created in the tumor. Cancer was thus believed to be just a disease characterized by a cell-autonomous press. However, it has been acknowledged that tumors are heterogeneous organs, made of a various number of stromal components which are crucial players and not just participants in the tumorigenic process.

The tumor microencironment (TME) is the cellular environment in which the tumor exists, including surrounding blood vessels, immune cells, fibroblasts, bone marrow-derived inflammatory cells, lymphocytes, signaling molecules and the extracellular matrix (ECM)[1,2]. The tumor and the surrounding microenvironment are closely related and interact constantly. Tumors can influence the microenvironment by releasing extracellular signals, promoting tumour angiogenesis and inducing peripheral immune tolerance, while the immune cells in the microenvironment can affect the growth and evolution of cancerous cells[3].

The tumor microenvironment features include hypoxia, acidosis, Hypo-nutrition and Inflammation. While hypoxia and acidosis have been described for decades as two ubiquitous features of the tumor microenvironment (TME), hypoxia is by far the more extensively studied[4]. The concept of hypoxia-induced angiogenesis and the associated hope for a new magic bullet treatment[5], as well as the well-characterized hypoxia-inducible factor (HIF)-driven gene reprogramming[6], have largely contributed to the current understanding of the determinants and biological consequences of tumor hypoxia.

However, with the recent impetus to study cancer metabolism, tumor acidosis is becoming increasingly recognized as another major hallmark of tumors. Indeed, the way we envision acidosis is shifting from a passive collateral effect resulting from tumor growth to a key regulator of tumor progression. In addition, if tumor acidosis results from the accumulation of H^+ ions in the extracellular matrix (ECM), it is an initial consequence of alterations in the pH of the cytosolic compartment of tumor cells, which cannot withstand acidification, as this impinges on the activity of the intracellular enzymatic machinery. H^+ ions may indeed directly influence the ionization of some amino acid residues within various proteins and thus alter their functions[7], eventually leading to cell death if excess H^+ ions are not removed. This underlines the delicate balance between the intracellular pH (pH_i) and the extracellular pH (pH_e) and points towards the metabolic preferences of cancer cells in a given tumour area as a trigger for various phenotypic adaptations that maintain the pH_i in an optimal range and at the same time determine the behaviour of cancer cells in their acidic extracellular environment.

Tumors are often challenged by a lack of glucose, as well as other nutrients, owing to poor vascularization upon quick expansion of the tumor mass. It is becoming clear that tumor cells can partly overcome this nutrient requirement to survive and grow in nutrient-deprivation microenvironments by exploiting the full array of nutrients available extracellularly, including low-molecular-mass nutrients as well as macromolecules and cellular debris[8]. In addition, cancer cells must also optimize nutrient utilization, which in turn induces cancer cell metabolism reprogramming. Furthermore, nutrient deprivation also contributes to several biological processes critical for cancer progression, including proliferation, migration/invasion and resistance to chemotherapy and radiotherapy. Thus, targeting cancer cell nutrient metabolism also constitutes a critical strategy required for the development of effective cancer therapies.

Inflammation occurs as a defensive response when a body with vessel system is exposed to invading pathogens as well as physical and chemical hazards. However, the relationship between inflammation and cancer is more complicated. The presence of leukocytes within tumours, observed in the 19th century by Rudolf Virchow, provided the first indication of a possible link between inflammation and cancer. Yet, it is only during the last decade that clear evidence has been obtained that inflammation plays a critical role in tumorigenesis, and some of the underlying molecular mechanisms have been elucidated[9]. A role for inflammation in tumorigenesis is now generally accepted, and it has become evident that an inflammatory microenvironment is an essential component of all tumors, including some in which a direct causal relationship with inflammation is not yet proven[10]. Only a minority of all cancers are caused by germline mutations, whereas the vast majority (90%) is linked to somatic mutations and environmental factors. Many environmental causes of cancer and risk factors are associated with some form of chronic inflammation. Up to 20% of cancers are linked to chronic infections, 30% can be attributed to tobacco smoking and inhaled pollutants (such as silica and asbestos), and 35% to dietary factors (20% of cancer burden is linked to obesity)[11].

Hypoxia-induced changes in cancer cell metabolism

The tumor microenvironment is often hypoxic. Hypoxia arises in tumors through the uncontrolled oncogene driven proliferation of cancer cells in the absence of an efficient vascular bed. Owing to the rapid proliferation of cancer cells, the tumor quickly exhausts the nutrient and oxygen supply from the normal vasculature, and becomes hypoxic. This drives upregulation of the production angiogenic factors from the hypoxic tumor sites[12], which triggers the vascularization of the tumor mass, a phenomenon that was first reported in 1908[13]. However, the vessels formed in tumours are not associated with the same careful co-ordination of pro-and anti-angiogenic factors as with normal physiological angiogenesis, and lead to vascular leakiness, chaotic architecture and non-laminar blood flow[14]. The resulting vessels are therefore not always functional, being either blunt ended or subject to changes in direction and velocity of flow. Finally, although the endothelial cells in normal vessels create a smooth, cobblestone-like surface that permits laminar non-thrombogenic flow, ebdothelial cells of tumor-associated vessels have gaps between them, resuling in non-laminar flow that makes the blood prone to clotting, and local tissue oedema[15,16].

Hypoxia is one of the most widely characterized properties of the tumor micoenvironment. A key mediator of adaptation to hypoxia is the transcription factor hypoxia-induced factors (HIFs). The HIF transcription fa[17]ctors are composed of a stable β subunit, and one of two oxygen-labile α subunits(HIF1α and HIF2α), the stability of the latter being controlled through hydroxylation by PHDs and subsequent binding and ubiquitylation by pVHL[18-20]. This leads to the rapid degradation of the α subunit in normoxic conditions through proteasomal activity. To transactivate target genes, the HIF transcription factors bind hypoxia-responsive elements that can be either

proximal or distal to the promoter of the target genes. Through this, they regulate the expression of a significant number if gene targets involved in angiogenesis, metabolic adaptation, survival and migration.[21-25]

It has been long appreciated that hypoxia contributes to cancer cell glucose fate metabolic changes (Figure1). Under hypoxic conditions, glycolytic rates are enhanced by up-regulating and/or activating a series of glycolysis-stimulating enzymes, including PFK, hexokinase II (HK2), pyruvate kinase M2 (PKM2), and lactate dehydrogenase A (LDH-A), which helps supply NAD+ for glycolysis[26,27]. Several acid and/or lactate-extruding transporters including monocarboxylate transporter (MCT) isoform 4 and the Na+/H+ exchanger NHE1 are also upregulated by hypoxia through HIF-1a signaling[28,29].

The net result is that lactate and other acid equivalents are extruded by the tumor cells in often greatly increased amounts. Interestingly, metabolic coupling occurs between cancer cells in hypoxic and well-oxygenated tumor regions, and between cancer cells and stromal cells. Specifically, it is proposed that lactate produced by hypoxic tumor cells is taken up via MCT1 in normoxic cancer cells, followed by conversion to pyruvate, sparing the limited supply of glucose for the hypoxic tumor regions[30].

Another hypoxia contribution to cancer cell metabolic is glutamine fate metabolic changes. Glutamine, the most abundant non-essential amino acid in blood, is central to the anabolism of most cells in normoxia, and its uptake exceeds that of any other amino acid around tenfold[31]. Under normoxic conditions, glutamine is oxidized to provide both ATP through the tricarboxylic acid cycle and anabolic building blocks for cell proliferation through fatty acid, amino acid and nucleotide synthesis. However, a consequence of decreased pyruvate oxidation and mitochondrial respiration during the cellular adaptation to hypoxia is increased dependence upon reductive glutamine flux for cell proliferation and viability.

In cells with defective mitochondria, or those in hypoxia, glutamine oxidation is decreased[32-35]. As a result, reductive glutamine metabolism has been proposed to occur in response to increases in the alpha-ketoglutarate (αKG)/citrate ratio and has since been implicated as an important pathway for the survival of these cells. Reductive carboxylation describes the synthesis of citrate using the reducing potential of NADPH via the enzymes isocitrate dehydrogenase (IDH) 1 and 2, and aconitase (ACO) 1 and 2 (Figure X). Notably, IDH1 and ACO1 are cytosolic enzymes, whereas IDH2 and ACO2 are mitochondrial, forming two pathways with the same activity but distinct localization. IDH-mediated reductive carboxylation of glutamine-derived αKG to produce sufficient citrate for lipid synthesis was first described in normal brown adipocytes[36] and is observed when steady-state αKG levels are high, and that of citrate is low[37,38]. The conditions required for a shift away from oxidative glutamine metabolism and an increase in reductive carboxylation during hypoxia are still unclear. It has been suggested that stabilization of HIF1 promotes seven in absentia homologue 2-targeted ubiquitination and proteolysis of the E1 subunit of the α-ketoglutarate dehydrogenase complex, resulting in reduced α-ketoglutarate dehydrogenase activity, decreased glutamine oxidation and therefore increased glutamine-dependent lipid synthesis, which is necessary for hypoxic cell proliferation[39].

Despite decreased mitochondrial respiration and increased activity of reductive carboxylation, hypoxic cells can maintain and in some cases even upregulate oxidative glutamine metabolism,

accounting for the majority of ATP synthesis through oxidative phosphorylation in these conditions[40-42]. It is thought that this activity also facilitates the production of mitochondrial NADPH through the activity of malic enzyme (ME), which converts malate to pyruvate, and is found to be expressed at high levels in some tumors[43,44]. Although this is likely an important source of mitochondrial NADPH in some circumstances, it is not clear what additional benefit mitochondrial ME activity provides in the presence of an active NNT. Instead, the reduction of malate to pyruvate in the cytosol by ME1, perhaps as part of a malatepyruvate shuttle in hypoxia (using pyruvate carboxylase), may provide a cytosolic source of NADPH[45]. Interestingly, in normoxia, neither ME, IDH1&2 nor NNT were shown to be major NADPH sources by small interfering RNA knockdown[45]. However, as genome-scale flux balance analysis by the same authors predicted a significant role for malic enzyme, it is likely that other pathways were capable of compensating in its absence[45].

Acidification-induced changes in cancer cell metabolism

A common distinguishing feature of solid tumors is the presence of an acidic extracellular environment. This arrives via the excretion of lactic acid (MCTs) but is also enhanced by CO2 hydration via the extracellular facing CAs. Thus tumor cells are required to deal efficiently with increased metabolic waste production to survive in their

potentially hostile environment. In the last few years, several studies have addressed how tumor acidosis may in turn influence tumor metabolic preferences[46-51]. Indeed, proton-venting cellular mechanisms have their own limitations, and above a certain threshold of ambient acidity, cancer cells need to profoundly rewire their metabolic preferences to maintain their pHi within the limits of cell viability. This is enabled by an extremely efficient pHi regulating mechanism that maintains tumor cell pHi in the alkaline range despite the acidic surroundings[52]. We have recently re-enforced that hypoxia provides a definite survival advantage for tumour cells experiencing acidosis[53]. This improved survival in hypoxia is a combination of enhanced pHi regulating capacities that can maintain sufficient ATP levels for cellular function. Tumor cell pHi regulation follows the classical models of either H^+ extrusion or $HCO3^-$ buffering of the cytoplasm[54]. A redundancy of pHi regulating proteins is evident in tumor cells with alterations in a few key players under hypoxia appearing to give tumor cells their pHi regulating advantage over normal cells[52].

Tumors secreting large amounts of lactate into TME may alter the cancer cell metabolism. One of the very first adaptations of tumor metabolism to TME acidosis is associated with the generation of a lactate gradient, with the highest concentrations found in the most hypoxic tumor areas. Several independent investigators have documented in a large variety of tumor cell types[30,55-59] that while lactate is released through MCT4 as the end-product of glycolysis, other cancer cells can capture lactate via MCT1 and consume it after conversion into pyruvate (Figure 2). This led to the concept of metabolic symbiosis between lactate-generating and lactate-consuming cells in solid cancers[60-63]. In light of the necessity for MCT1 to co-transport H+ ions with lactate for inward flux, this process further supports the need to neutralize intracellular H+ ions to maintain the lactate shuttle. Intracellular and extracellular CA activities may fulfil this role by promoting the neutralization of H^+ ions and the hydration of CO2, respectively (Figure 2).

A transcriptional H^+-responsive element that could reprogram gene expression has not been reported thus far. However, several studies have identified HIF2α as a key regulator of metabolic adaptation to acidosis[48,49,64,65], while the activity of HIF1α, the *bona fide* hypoxia-induced transcription factor, was generally found to be downregulated[48,66,67]. In addition to opposing changes in HIF isoform abundance, acidosis leads to an NAD+-dependent increase in the activity of the histone deacetylases sirtuin 1 (SIRT1) and SIRT6, which in turn supports the differential effects on the activity of both HIFs40. Deacetylation of lysine residues in the HIF2α amino-terminal transactivation domain (N-TAD) region is associated with increased transcriptional regulatory activity[68], whereas similar deacetylation in HIF1α prevents p300 recruitment and represses HIF1α transcriptional activity[69]. In cancer cells of the cervix, colon and pharynx, HIF2α upregulation and activation under acidic conditions were shown to drive glutamine metabolism via an increase in the expression of the glutamine transporter ASC-like Na+-dependent neutral amino acid transporter 2 (ASCT2) (also known as SLC1A5 and ATB(0)) and glutaminase 1 (GLS1) in replacement of the preferred glucose metabolism observed at neutral pH [48]; HIF1α target genes were instead down-regulated under acidosis, leading, for instance, to a dramatic reduction in the expression of the glucose transporter GLUT1 (also known as SLC2A1) and MCT4.

Another very striking alteration in cancer cell metabolic preferences under acidosis is related to lipid metabolism. Acidosis-driven reductive carboxylation of glutamine-derived α-ketoglutarate was shown to contribute to fatty acid synthesis (FAS) via the production of acetyl-CoA from citrate[48]. Acetate was also identified as a source of acetyl-CoA to synthesize fatty acids under acidosis in response to activation of sterol regulatory element-binding protein 2 (SREBP2) and consecutive up-regulation of acyl-CoA synthetase short-chain family member 2 (ACSS2)[51]. While the above two FAS-supporting pathways were also reported to be stimulated in response to hypoxic stress[34,35,39,70], a major difference compared with hypoxic conditions is the concomitant stimulation of fatty acid oxidation (FAO). In various cancer cells, including those from colon, oropharyngeal and cervical tumors, this capacity to simultaneously exploit FAS and FAO was shown to be promoted under acidosis by the down-regulation of acetyl-CoA carboxylase 2 (ACC2) [47](which normally prevents the degradation of neo-synthesized fatty acids in healthy tissues). Moreover, besides fuelling the TCA cycle, FAO-derived acetyl-CoA leads to a dramatic increase in the non-enzymatic acetylation of many proteins, including electron transport chain (ETC) complex members[47]. Inhibition of the activity of acetylated ETC complex I has been measured in acidosis-adapted cancer cells of different origins[47]. Although ETC inhibition may appear counterintuitive with regards to the observed increase in mitochondrial respiration driven by FAO, restraining complex I activity was documented to limit reactive oxygen species (ROS) production as a consequence of mitochondrial overfeeding[47] without completely blocking OXPHOS.

ROS production is also a common issue for cells exposed either to acute episodes or prolonged periods of acidosis.

However, phenotypic differences do exist, as cancer cells chronically exposed to acidic pH proliferate (at a similar rate to that of the same cancer cells maintained at neutral pH)[48], while acute exposure to acidosis is associated with growth inhibitory effects and a concomitant dramatic decrease in the conversion of glucose to ribose for ribonucleotide synthesis[71]. Interestingly, under these acute acidosis conditions, glutamine and fatty acids were shown to contribute to ribose synthesis, but this contribution was insufficient to compensate for the loss of glucose metabolism[71]. This underlines the progression in the adaptation to acidosis, with cancer cells first developing strategies to cope with the demand for bio-energetic and antioxidant needs necessary for survival and then acquiring the capacity to meet biosynthetic requirements (that is, ribonucleotides, lipids and proteins) for proliferation.

The secreted lactate could have supporting roles for the cancer cells. First, local acidification of the tumor microenvironment could potentially support tumor invasion[72], in part through an increase in the level of extracellular VEGFA[73,74] and proteases[75,76]. Second, the lactate can be taken up by adjacent stromal cells and used as an energy substrate to support growth or to genenrate pyruvate, which is then extruded by the stroma and taken up by the cancer cells[61,77]. Under conditions of low glucose availability, cancer cells can use the extracellular lactate or pyruvate to support the TCA cycle and to provide citrate and acetyl-CoA for fatty acid synthesis.

Finally, it is worth noting that important insights into the signalling pathways transducing extracellular acidosis to gene reprogramming will probably arise from the emerging field of pH sensors[78]. G protein-coupled receptors (GPCRs), including GPR4, GPR65 (also known as TDAG8) and GPR68 (also known as OGR1), are indeed reported to be activated through the protonation of histidine residues located within the extracellular portion of these receptors[79]. These pH-sensing receptors were documented to transduce signals through different G proteins and activate various pathways, including phospholipase C (PLC) and adenylyl cyclase[80]. The non-GPCRs, transient receptor potential V1 (TRPV1) and acid-sensing ion channel 1 (ASIC1) were also reported to sense extracellular acidic pH [80]. Calcium influx directly or indirectly resulting from the opening of these channels was recently reported to account for nuclear factor-κB (NF-κB) activation in acidosis-exposed breast[81] and prostate[82] cancer cells. Furthermore, because of the charged nature of some residues, including histidine and arginine, pH sensing can also directly arise from changes in the protonation of various signalling proteins[7,83] (that is, independently of pH-sensing receptors or channels). This is supported by the pH-sensitive activity of several glycolytic enzymes[83] as well as mutations altering the activity of critical proteins. For instance, the arginine-to-histidine substitution R337H in the tetramerization domain of the tumor suppressor protein p53 leads to inhibition of DNA binding in the presence of an increased pHi[84]. Uncovering the signalling pathways as well as the subset of genes whose expression is altered in response to the activation of pH sensors represents one of the most exciting challenges in the field of tumour acidosis.

Hypo-nutrition-induced changes in cancer cell metabolism

Rapidly proliferating tumors cells require an abnormally enhanced nutrient supply to support their increased bioenergetics and demand for carbon building blocks compared to normal cells. In order to overcome this nutrient requirement, cancer cells must also optimize nutrient utilization when resources are scarce. Recent work has highlighted the importance of metabolic flexibility in both cultured cells and *in vivo*. For example, glucose deprivation, or growth in the harsh environment of the subcutaneous space in mice, elicits a selective pressure for *KRAS* mutations in colon cancer cells[85]. In this context, mutated *KRAS* rendered cells tolerant of low glucose conditions. Similarly, cancer cells in culture can restructure their metabolism to compensate for the loss of either glucose or glutamine, often using one nutrient to fill metabolite pools normally supplied by the other[40,86,87]. High-throughput screens revealed that cells chronically exposed to low glucose require oxidative phosphorylation as a means to maintain growth[88]. In a similar vein, subsets of lymphoma preferentially use, and can be highly dependent on, oxidative metabolism rather than the more classical glycolytic phenotype[89].

Although most cultured cancer cells use glutamine to supply the oxaloacetate (OAA) pool, complementing glucose-dependent acetyl- CoA formation, glutamine's ability to fuel alternative forms of metabolism has emerged as an important component of cell survival. Glucose deprivation in Myc-enhanced lymphoma cells stimulates a pathway whereby glutamine carbon is re-routed to acetyl-CoA[40], and which can be mimicked by silencing the mitochondrial pyruvate carrier (MPC)[90,91]. This pathway is dispensable in glucose-replete cells with normal MPC function, but essential for survival and tumor growth when MPC is impaired[91], indicating the importance of this mode of glutamine oxidation during nutrient limitation.

Glutamine deprivation also induces metabolic vulnerabilities. Citrate synthase loss was found to protect cells against apoptosis during glutamine deprivation[92]. Normally, citrate synthase condenses glutamine-derived OAA with acetyl-CoA to maintain TCA cycle function[43]. However, when glutamine is scarce, shunting OAA towards asparagine rather than citrate suppresses the unfolded protein response and supports cell survival[92]. Exogenous asparagine mimics citrate-synthase silencing during glutamine withdrawal. Although asparagine is normally considered a non-essential amino acid, rapidly proliferating cells need an abundant supply for protein synthesis, which is the basis of l-Asparaginase use in cancer therapy[93,94]. Because expression of asparagine synthetase correlates with poor prognosis in glioma and neuroblastoma[92], these findings suggest that the ability to maintain an asparagine pool may provide an advantage to tumour cells *in vivo*.

Other mechanisms also enable cancer cells to deal with glutamine deprivation. Commisso *et al.* demonstrated that glutamine deprivation stimulates macropinocytosis in Ras-expressing cancer cells[95]. This process enables cells to scavenge fluid and macromolecules, using a system of membrane ruffling to capture and incorporate extracellular material. Extracellular proteins were identified as important components of the cargo captured and internalized in macropinosomes, allowing starved cells to generate pools of glutamine and other amino acids to supply the TCA cycle[95]. This mechanism relieved cells with oncogenic *KRAS* or Src from dependence on extracellular glutamine, and was required for maximal growth of *KRAS* tumours *in vivo*. Thus, macropinocytosis provides a mode of metabolic flexibility enabling some transformed cells to compensate for interruptions in the extracellular supply of free amino acids.

In addition to scavenging extracellular protein, cancer cells also activate autophagic degradation of macromolecules when deprived of nutrients or of the signals that stimulate nutrient uptake[96-99]. During autophagy, damaged organelles and their macromolecular components are degraded, providing recycled small molecule nutrients to feed intermediary metabolism[98,100,101]. Autophagy may also function to eliminate defective mitochondria, thereby reducing accumulation of reactive oxygen species (ROS) and improving cellular fitness. In Ras- or BRaf-driven mouse models of cancer, autophagy is crucial for tumour growth and/or progression. *KRAS*-driven pancreatic tumours in mice require autophagy for maximal growth[102], and loss of essential autophagy genes impairs mitochondrial function in *KRAS*-driven lung tumours[103,104]. Interestingly, impaired autophagy results in the formation of oncocytomas, benign tumours filled with damaged mitochondria[103]. This implies that formation of aggressive *KRAS*-driven carcinomas requires both autophagy and effective mitochondrial function. Autophagy is also essential for maximal growth of BRaf`V600E` lung tumours, and inhibiting autophagy extends the survival of mice bearing these tumors[105]. Furthermore, although chronic ablation of the autophagy gene *Atg7* causes a number of systemic effects in mice, acute *Atg7* deletion specifically impaired growth of pre-existing *KRAS*-driven lung tumors prior to the appearance of pathology in normal tissues[106]. Overall, these findings emphasize a role for autophagy in driving aggressive tumor formation and maintenance by providing an intracellular nutrient supply to support cell survival and growth.

Inflammation-induced changes in cancer cell metabolism

While acute, transitory inflammation is an essential actor of tissue damage control and repair, tumor-associated inflammation- which occurs in virtually all tumors- is of a chronic, unresolved type[107] that fosters tumor progression. During tumorigenesis, cancer cells, innate immune cells [such as dendritic cells or tumor-associated macrophages (TAMs)] and activated resident cells [such as cancer-associated fibroblasts (CAFs) or endothelial cells] produce a variety of cytokines and chemokines in response to the danger signals originating from the tumor. These soluble factors drive the recruitment of massive amounts of additional bone marrow-derived innate immune cells, which fuel the so-called cytokine storm[108]. This prolonged reaction favors tumor cell survival and proliferation, immunosuppression (by the inhibition of effector immune cells and the accumulation of myeloid suppressive cells) and angiogenesis[109]. Promisingly, multiple anti-inflammatory agents are under development and/or under clinical testing currently in chemoprevention trials[108].

Inflammation was one of the first biological processes to be suspected of having a strong connection with tumor development. It was the first time that components other than cancer cells were being investigated with regards to their support in tumor progression. The link between inflammation and cancer was later associated with the presence of a high number of leukocytes in tumor tissues. Today it is recognized that the chronic inflammation plays a major rule in tumor initiation, settlement, and in the invasion of other body sites[110].

Various publications had pointed out the role of each component, particularly TAMs, CAFs and endothelial cells, in the promotion of tumor growth and the progression of cancer. Instead of fighting against cancer like most other cells in the tumor microenvironment, M2 macrophages are polarized by cancer-derived factors to promote tumor growth, immunosuppression, and metastasis. Therefore, the knowledge of pathways involved in the maintenance and control of the tumor microenvironment will provide a better-improved understanding of cancer biology, and open new opportunities for much more specific targets for cancer therapy[111,112].

Inflammatory mediators are often highly expressed in a tumor microenvironment. It is now very known that chronic inflammation participates enormously in tumorigenesis. Tumor-derived molecules are responsible for the activation of inflammatory cells like macrophages and fibroblasts. Macrophages in the tumor microenvironment come from the differentiation tumor-resident macrophages and from monocytes recruited from blood vessels. The differentiated macrophages are then polarized in tumor-associated macrophages. There are two known phenotypes for TAMs, which are M1 macrophages (pro-inflammatory macrophages) and M2 macrophages (anti-inflammatory macrophages)[113]. As for cancer-associated fibroblasts, they are obtained from normal fibroblasts already present in the tissue. The CAFs acquire specific characteristics similar to myofibroblasts. Both TAMs and CAFs are the most present cells in the tumor microenvironment. Various studies have highlighted how both cells play a crucial role in tumor ignition, progression, evasion, and resistance to chemotherapy[114].

In the tumor microenvironment, TAMs and CAFs are involved in the evolution of a tumor by the production of cytokines. Some cytokines are common to both cells, such as IL-6, IL-8, IL-10, and IFN-γ, but they also produce different cytokines[115]. Cytokines play a major role in the development of chronic inflammation and in the anti-tumor response, but also participate in all steps of cancer progression via inflammation[116]. In addition to the production of keys mediators for tumor growth, inflammation can activate autophagy[117].

Conclusions and Perspective

Microenvironment stress can induce cancer cell metabolism reprogramming, which improves cellular fitness to provide a selective advantage during tumorigenesis. Most of the classical examples of reprogrammed activities either support cell survival under stressful conditions or allow cells to grow and proliferate at pathologically elevated levels. It logically flows that if these activities provide benefit to the malignant cell, then some might represent suitable therapeutic targets. This rendering of cancer metabolism is supported by many examples in which inhibition of an enhanced metabolic activity results in impaired growth of experimental tumors.

Although our knowledge of metabolic transformation in cancer has improved markedly over the past decade, the impact of microenvironment stress on most cellular metabolic pathways is still not entirely clear. Several challenges will likely shape research over the next years. First, the studies cited were performed primarily in cancer cell lines rather than intact tumors. These straightforward experimental models have been highly informative regarding the molecular mechanisms of metabolic reprogramming, particularly those linking aberrant signaling to altered metabolic fluxes. However, it is challenging to model an accurate TME in culture. Direct analysis of metabolic fluxes in intact tumors should begin to play a more prominent role in the field and may prove essential in determining precisely how to deploy metabolic inhibitors in clinical trials. Developing rational therapeutic strategies will be aided by learning how to derive metabolic information efficiently and comprehensively from both preclinical and clinical models of intact tumor growth. Secondly, too few candidates for a targetable, tumor-specific metabolic activity are available; this has stimulated intense interest in finding additional metabolic alterations for which the therapeutic window may be sufficiently wide for real clinical opportunities. Third, although we have learned a great deal regarding the metabolic pathways that support cancer cell proliferation, we know much less about the metabolism that supports the survival of non-proliferating tumor cells, which constitute the bulk of the malignant cells in most solid tumors. Along these lines, the metabolism of CSCs is just now beginning to be investigated, and it will be of major interest to devise strategies to target metabolism in these cells. Finally, we still know relatively little about the metabolic interactions between tumor and host. This area has the potential for enormous impact on public health. Thus, overcoming several or many of these challenges will likely provide an effective approach to cancer target therapy.

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Conflict of Interest statement

The authors declare that there are no conflicts of interest.

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