Review

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The Role of Oxidative Metabolism in Tumorigenesis and Drug Resistance

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Aerobic glycolysis, i.e., non-oxidative glycolysis occurring under aerobic conditions (the so-called Warburg effect) is now recognized as a hallmark of cancer. However, evidence increasingly indicates that upregulated oxidative metabolism is also pivotal in tumorigenesis. In this article, we discuss factors that upregulate oxidative metabolism in tumor cells. These factors are associated with tumor cell-intrinsic and -extrinsic stimuli including antitumor drugs, requirements related to the different steps of tumorigenesis (initiation and acquisition of cancer stem-like cell functions, primary tumor growth, quiescence, metastatic dissemination), factors related to the phenotypic changes of tumor cells (e.g., autophagy and epithelial-mesenchymal transition), and particular metabolic requirements of proliferating tumor cells. In this context, we also discuss drug resistance associated with upregulated oxidative metabolism. We conclude by proposing a model whereby these factors, either individually or in combination, promote upregulation of oxidative metabolism. In the following, we address some mechanistic aspects that underlie the upregulation of oxidative metabolism and discuss the consequences on tumor prognosis. In the conclusion section of this article, we discuss possible therapeutic implications of the knowledge gathered in this field over the years.

Keywords: oxidative metabolism; lactogenesis; drug resistance; metastasis; tumor initiation; tumor growth

Introduction

Cells produce energy in the form of adenosine triphosphate (ATP) through two metabolic pathways: the tricarboxylic acid (TCA) cycle-oxidative phosphorylation (OXPHOS) pathway (hereafter oxidative metabolism) and the glycolytic pathway. Under aerobic conditions, glucose fuels oxidative metabolism upon conversion to pyruvate but, in anaerobic conditions, it undergoes fermentation to lactate, a reaction referred to as anaerobic glycolysis (Fig. 1). Almost a century ago, Otto Warburg [1] observed that glycolysis in cancer cells is upregulated and can also generate lactate under normoxic conditions, a phenomenon referred to as aerobic glycolysis or the Warburg effect. In this article, I will refer to lactate-generating metabolism as lactogenic metabolism. Fig. 1 provides a picture of these two energy-producing pathways and of the associated pathways that are discussed in this article. A more complete representation can be found in biochemistry textbooks or Ref. [2]. Herein, some key aspects of these two pathways are briefly addressed to provide background for the further reading of the article [2]. An important node that connects glycolytic and oxidative metabolism is represented by the enzyme pyruvate dehydrogenase (PDH) which decarboxylates pyruvate to acetyl-CoA and drives its entrance into the TCA cycle with concomitant generation of reduced nicotinamide adenine dinucleotide (NAD). This step is tightly controlled since another enzyme, pyruvate dehydrogenase kinase, inactivates PDH by phosphorylating it. Whereas glucose is certainly one of the main fuels that feed the TCA cycle upon transformation to pyruvate, there are some other important molecules that can feed the TCA cycle, in particular acetyl-CoA, glutamine, and lactate. Acetyl-CoA, besides being generated from glucose, is also generated by the breakdown of fatty acids through β-oxidation and condenses with oxaloacetate to generate citrate; glutamine enters the TCA cycle upon conversion to α-ketoglutarate; lactate can enter the TCA cycle upon reversible conversion to pyruvate.

Oxidative metabolism is much more efficient in generating ATP than lactogenic metabolism (a net of 2 ATP molecules in lactogenic metabolism per glucose molecule compared to $\sim$30 in oxidative metabolism). Not surprisingly, then, oxidative metabolism generates more than 90% of ATP in aerobic conditions [3]. This raises the question as to why tumor cells often resort to lactogenic metabolism in order to produce energy. Several explanations have been put forward. Thus, despite its low efficiency in ATP yield, glycolysis can produce ATP at a faster rate than oxidative metabolism [4]. Moreover, glycolysis may give rise to increased levels of intermediate metabolites which can feed side metabolic pathways, like the pentose phosphate pathway (PPP), that support tumor cell proliferation [5]. Upregulated glycolysis and lactogenic metabolism can also induce epigenetic changes that can promote tumorigene-

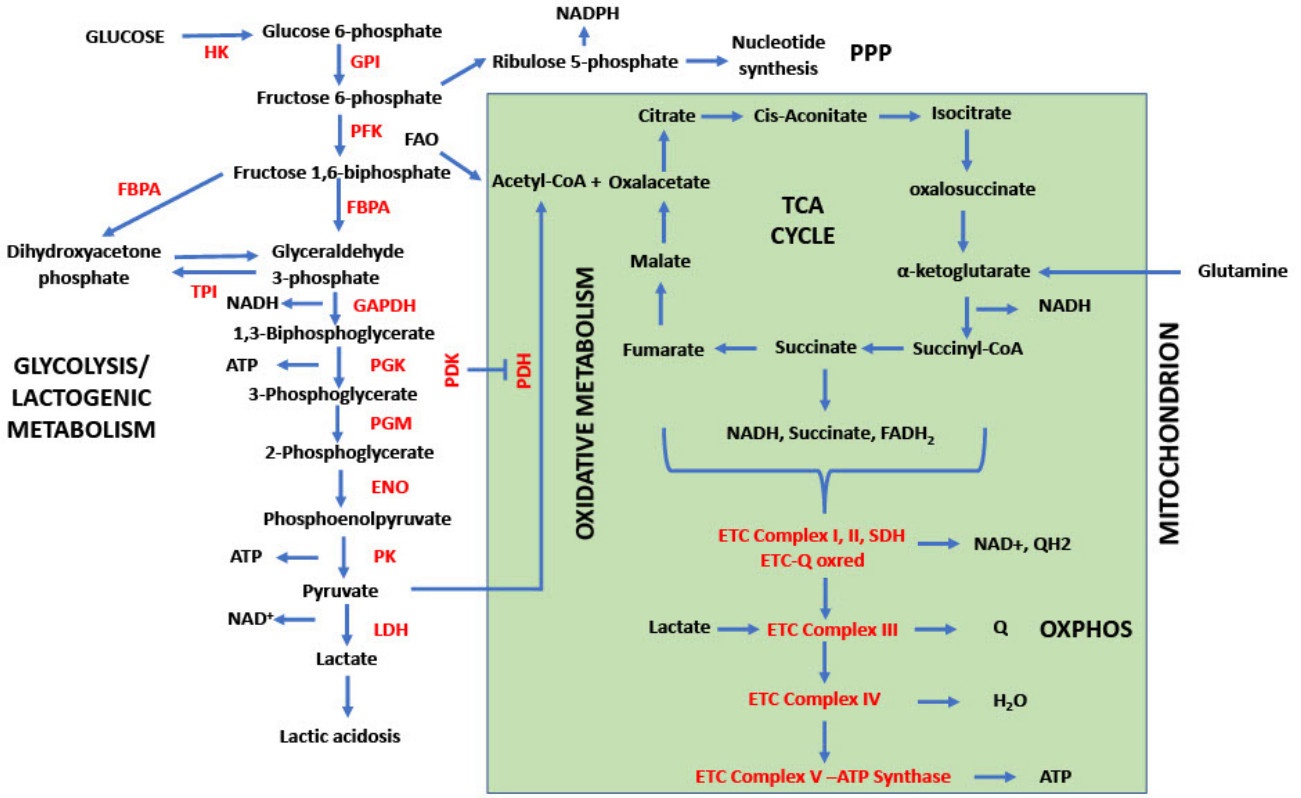

Fig. 1. A simplified view of the two energy-producing metabolic pathways, glycolysis/lactogenic metabolism and oxidative metabolism (TCA cycle and OXPHOS). Enzymes are in red, and metabolites and other outputs are in black. ATP, adenosine triphosphate; ENO, enolase; ETC, electron transport chain; FBPA, fructose-biphosphate aldolase; $FADH_2$, reduced flavin adenine dinucleotide; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GPI, glucose 6-phosphate isomerase; HK, hexokinase; LDH, lactate dehydrogenase; NAD^+, oxidized nicotinamide adenine dinucleotide; NADH, reduced NAD; NADPH, reduced nicotinamide adenine dinucleotide phosphate; OXPHOS, oxidative phosphorylation; oxred, oxidoreductase; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PFK, phosphofructo-2-kinase; PGK, phosphoglycerate kinase; PGM, phosphoglycerate mutase; PK, pyruvate kinase; PPP, pentose phosphate pathway; Q, ubiquinone; QH2, ubiquinol; SDH, succinate dehydrogenase; TCA, tricarboxylic acid; TPI, triosephosphate isomerase. The figure was created with PowerPoint 2021.

sis [6]. By inducing global histone acetylation and "lactylation" [7,8], chromatin accessibility is enhanced, thereby facilitating DNA repair and increasing the expression of oncogenes.

Metabolic Heterogeneity

We have mentioned that oxidative or lactogenic metabolism may predominate over each other pathway in tumor cells. It is important to stress, however, that, even if one pathway predominates, both metabolic pathways are active, i.e., tumor cells are characterized by metabolic heterogeneity [9]. Accordingly, a circuit analysis showed that tumor cells exist in a hybrid, oxidative/lactogenic metabolic state that allows them to adapt to different microenvironmental conditions [10]. Another study showed that tumor cells with a hybrid oxidative/metabolic phenotype used both pathways for energy production and generation of intermediates for biomass production and that this hybrid phenotype was associated with metastasis and drug resistance [11]. There is also evidence that oxidative metabolism is mainly used in the G1 phase and lactogenic metabolism in the S phase of the cell cycle [12,13]. In breast cancer cells, a switch from oxidative to lactogenic metabolism impaired tumorigenesis, suggesting that, at least in some circumstances, upregulated lactogenic metabolism is not sufficient to support tumor growth in the absence of oxidative metabolism [14].

Metabolic heterogeneity exists also between different tumor cells of the same tumor, or of different tumors of the same type. Thus, among acute myeloid leukemia (AML) cell lines derived from patient-derived xenografts, some showed a predominantly oxidative metabolism, while other cell lines showed a low oxidative metabolism, and only cell lines with a predominantly oxidative metabolism were resistant to cytarabine *in vivo* [15]. In another study, different leukemia cell lines were shown to rely predominantly on either lactogenic metabolism or oxidative metabolism

[16]. Metabolic heterogeneity was also found in a study that investigated 13 established and 12 patient-derived ovarian cancer (OC) cell lines. Cell lines with a predominantly lactogenic phenotype were chemosensitive, whereas chemoresistant cells showed metabolic plasticity with the ability to switch between lactogenic and oxidative metabolism [17]. In another study, the proliferation of one tumor cell line (U251) depended mainly on lactogenic metabolism, whereas other tumor cell lines relied predominantly on oxidative metabolism [18]. Under conditions of serum starvation, lactogenic metabolism was further reduced and oxidative metabolism was upregulated. Patient-derived melanoma cell lines and patient samples showed metabolic alterations that varied greatly, both quantitatively and qualitatively, with some cell lines showing only altered lactogenic or oxidative metabolism [19]. Patients with pancreatic ductal adenocarcinoma (PDAC) were very heterogeneous with respect to their oxidative metabolism rates, and tumors with elevated oxidative metabolism were enriched in mitochondrial electron transport chain (ETC) complex I [20]. High-grade serous OC has been divided into two subgroups, one (referred to as low-OXPHOS) showing a predominantly lactogenic metabolism, and the second (referred to as high-OXPHOS) relying mainly on oxidative metabolism [21]. Interestingly, and in contrast to many reports that will be discussed later, high-OXPHOS tumors exhibited an increased response to chemotherapeutics.

These results show that metabolic heterogeneity can exist both within and between tumor cells and tumors. Moreover, it has been shown that the same tumor cells can switch from a predominantly oxidative to a predominantly lactogenic metabolism and vice versa. Thus, using two triple-negative breast cancer (TNBC) cell lines and one non-TNBC breast adenocarcinoma cell line, it was found that under normoxia OXPHOS was 2-times higher in the two TNBC cell lines than in the non-TNBC cell line. The latter depended equally on both pathways for ATP generation. When the cells were exposed to hypoxia, glycolysis was upregulated and OXPHOS was downregulated in all cell lines [22]. This is not surprising since hypoxia is the prototypic stimulus that induces a switch from oxidative to anaerobic, lactogenic metabolism [23]. Similarly, 3 cisplatin-resistant cell lines relied on fatty acid oxidation (FAO) and glutaminolysis for survival and proliferation under normoxic conditions, whereas they became more dependent on lactogenic metabolism under hypoxic conditions [24]. OC cells resistant to platinum-based agents switched between lactogenic and oxidative metabolism, depending on which pathway was better able to support tumor growth and chemoresistance [25]. Downregulation of lactogenic metabolism with a lactate dehydrogenase A (LDHA) inhibitor promoted a switch towards oxidative metabolism [26]. T-cell acute lymphoblastic leukemia (T-ALL) cells with activating NOTCH1 mutations relied mainly on glutaminolysis and oxidative metabolism for proliferation and growth [27]. Inhibition of NOTCH1 induced a metabolic collapse which was rescued by phosphatase and tensin homolog (PTEN) loss and consequent activation of lactogenic metabolism. In another study, ATP generation from lactogenic or oxidative metabolism was measured in 9 randomly selected tumor cell lines. Lactogenic and oxidative metabolism generated 23.7%–52.2 % and 47.8%–76.3% of total ATP, respectively [28]. When these cell lines were exposed to lactic acidosis, lactogenic metabolism and oxidative metabolism generated 5.7%–13.4% and 86.6%–94.3% of total ATP, respectively. In other words, ATP generation through oxidative metabolism was slightly predominant over that generated by lactogenic metabolism under normal conditions, whereas exposure to lactic acidosis led to a clear predominance of oxidative metabolism over lactogenic metabolism. This result, which is in line with previous observations that tumor cells can use lactate as an energetic fuel [29], is of particular interest because lactic acidosis in the tumor microenvironment is the consequence of lactogenic metabolism in tumor cells. Thus, lactogenic metabolism can induce metabolic reprogramming towards oxidative metabolism in tumor cells that become exposed to lactic acidosis. Similar experiments were performed with two lung adenocarcinoma (A-549, A-427) cell lines and non-transformed fibroblasts (MRC-5). All cell lines tested used lactogenic and oxidative metabolism to obtain energy [30]. Exposure of the tumor cell lines to lactic acidosis reduced lactogenic metabolism, while oxidative metabolism was increased in one case (A-427), but diminished in the other (A-549).

Factors Involved in the Upregulation of Oxidative Metabolism in Tumor Cells

Tumor Cell-Intrinsic or -Extrinsic Stimuli

Oxidative metabolism can be upregulated and become predominant in response to tumor cell-intrinsic or -extrinsic stimuli. This is not dissimilar to what has been reported for lactogenic metabolism [31]. In the following, we list and briefly discuss some of these stimuli (Table 1, Ref. [11,15,21,24–26,28,30,32–92]). As will be seen, some of them play a causative role in neoplastic transformation, while others are the consequence of neoplastic transformation and tumor growth.

Regarding tumor cell-intrinsic stimuli, these are oncoproteins or proteins that are overexpressed during tumorigenesis [93], including C-MYC [32,33], B-Raf [34, 35], Kirsten rat sarcoma virus (KRAS) [36], neuroblastoma RAS (NRAS) [35], mutated NOTCH1 [37], myeloid cell leukemia 1 (Mcl-1) [33], mutations of a component [switch/sucrose non-fermentable (SWI/SNF) related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4 (SMARCA4)] of the SWI/SNF chromatin remodeling complex [38], inactivating mutations/loss of tumor suppressor proteins [39,40],

the insulin-like growth factor-2 mRNA-binding protein 3 (IGF2BP3)-cytochrome c oxidase subunit 6B2 (COX6B2) axis [41], spleen tyrosine kinase (SYK) [42], small ankyrin 1 (sANK1) [43], ferredoxin reductase [44], BR serine/threonine kinase 1 (BRSK1) [45], NAD-dependent deacetylase sirtuin (SIRT)-3, mitochondrial deacetylase [46], neurolysin [47], leucine-rich pentatricopeptide repeat containing (LRPPRC) protein [48], the reduced NAD oxidase apoptosis-inducing factor mitochondria associated 2 (AIFM2) [49], the mitochondrial-specific protein caseinolytic protease P (CLpP) [50], increased secretion of thioredoxin-1 [51], upregulation of the glycolytic enzyme pyruvate kinase isoform M1 (PKM1) [52,53], chronic oxidative stress [21], elevated nicotinamide metabolism [54].

Many tumor cell-extrinsic stimuli that upregulate oxidative metabolism are generated as a consequence of tumor cell proliferation and tumor growth, including lactic acidosis [28,30,55–62], glutamine addiction [63], non-tumor cells from the TME-like bone marrow stem cells (BMSCs) [64], bone marrow mesenchymal stem cells [65], cancer-associated fibroblasts [11], differences between tumor cells growing *in vitro* and *in vivo*, with the latter being more dependent on oxidative metabolism than the former [66], nutrient deprivation [67–69], cell surface receptors like CD39 [70].

Although we know which stimuli, either cell-intrinsic or -extrinsic, can upregulate oxidative metabolism, it is unclear which properties these stimuli must possess in order to upregulate oxidative metabolism in tumor cells, compared to similar stimuli that upregulate lactogenic metabolism. Some indications have emerged in recent years. For example, it has been reported that *RAS* pathway mutations upregulate FAO and, consequently, oxidative metabolism [71]. These observations suggest that some stimuli are intrinsically endowed with the capacity to upregulate oxidative metabolism in tumor cells through mechanisms that remain to be elucidated. An alternative possibility, not incompatible with the previous one, is that a given stimulus upregulates oxidative metabolism depending on the tumor cell phenotype on which it acts, as will be discussed in more detail in the following sections.

Drug-Induced Upregulation of Oxidative Metabolism and Associated Drug Resistance

One class of extracellular stimuli that upregulate oxidative metabolism is antitumor drugs. Moreover, upregulated oxidative metabolism itself may be conducive to drug resistance. This knowledge is of obvious therapeutic relevance and we will discuss it in this section.

Different classes of antitumor drugs can upregulate oxidative metabolism in tumor cells, including chemotherapeutics [15,24,25,70,72–76], targeted therapeutics like anti-vascular endothelial growth factor (VEGF) monoclonal antibodies (mAb) [67], Aurora kinase A inhibitors [77], tyrosine kinase inhibitors (TKI) [78–82], serine-threonine kinase inhibitors [35,83–86], phosphoinositide 3-kinase (PI3K) inhibitors [87], histone deacetylase inhibitors (HDACis) [88,89], proteasome inhibitors [26,88,90], nicotinamide phosphoribosyltransferase (NAMPT) inhibitors [91], and irradiation [92].

As already mentioned, upregulated oxidative metabolism can induce drug resistance. Thus, antitumor drugs can induce resistance to themselves through upregulation of oxidative metabolism. Resistance can occur towards several different classes of antitumor drugs, and in the following, we will discuss examples for each of these classes.

Tumor cell-associated oxidative metabolism has been shown to induce resistance against chemotherapeutics. Thus, OC cells showed upregulated OXPHOS in response to doxorubicin and supported ATP-consuming drug efflux effected by the ATP binding cassette subfamily B member 1 (ABCB1) efflux pump [73]. OXPHOS upregulation was also observed in several chemoresistant human cell lines, and this was accompanied by greatly increased ATP production [94]. Similar results were also described with other chemoresistant cancer cells which relied on mitochondrially derived ATP to fuel ATP-binding cassette transporters that affected drug efflux [95]. In addition, chemoresistance associated with oxidative metabolism was induced in a wide range of different tumor types and against a broad range of chemotherapeutics through mechanisms of action that do not appear to involve drug efflux pumps: in AML cells by bone marrow stromal cells via activation of the interleukin (IL)-6/signal transducer and activator of transcription 3 (STAT3)/OXPHOS pathway [96]; in AML cells to cytosine arabinoside (Ara-C) via SIRT3 [46]; in AML cells to daunorubicin and Ara-C [15,70,74]; in ovarian SKOV3 cancer cells to cisplatin in response to B-cell lymphoma 2 (BCL-2)-driven upregulation of oxidative metabolism [97]; to irinotecan in non-small cell lung cancer (NSCLC) cells [75]; to cisplatin in lung cancer and melanoma cells [51,76,85]; to docetaxel in cells from advanced prostate cancer tissues [43]; to DNA-damaging agents, but not taxanes, in TNBC cells and tumors surviving chemotherapy [72]; and to oxaliplatin and 5-fluorouracil (5-FU) in colorectal cancer (CRC) cells [52,53].

Tumor cell-associated oxidative metabolism has also been shown to promote resistance against targeted drugs. Thus, inhibition of OXPHOS with a compound that blocks the activity of the ETC complex I inhibited tumor growth and augmented the efficacy of the MEK inhibitor trametinib [98]. Glioblastoma multiforme (GBM) cells resistant to the HDACi panobinostat and the proteasome inhibitor marizomib showed increased levels of TCA cycle metabolites and enzymes [88]. Upregulated oxidative metabolism caused resistance to the BCL-2 antagonist venetoclax in multiple myeloma (MM) patients with the 11;14 translocation, and inhibitors of mitochondrial respiration sensitized resistant MM cells to venetoclax [99]; to the Bruton's TKI

Table 1. Tumor cell-intrinsic or -extrinsic stimuli that upregulate oxidative metabolism.

	Type of stimulus (oncoproteins, overexpressed proteins, other stressors)	References
Tumor cell-intrinsic stimuli	C-MYC	[32,33]
	B-Raf	[34,35]
	NRAS	[35]
	KRAS	[36]
	Mutated NOTCH1	[37]
	MCL1	[33]
	Mutated SMARCA4	[38]
	Deficiency of the tumor suppressor retinoblastoma protein (Rb)	[39,40]
	IGF2BP3-COX6B2 axis	[41]
	SYK	[42]
	sANK1	[43]
	Ferredoxin reductase	[44]
	BRSK1	[45]
	SIRT3	[46]
	Neurolysin	[47]
	LRPPRC	[48]
	AIFM2	[49]
	CLPP	[50]
	Thioredoxin-1	[51]
	PKM1	[52,53]
	CD39	[70]
	Chronic oxidative stress	[21]
	Elevated nicotinamide metabolism	[54]
	Type of stimulus from the tumor microenvironment	
Tumor cell-extrinsic stimuli	Lactic acidosis	[28,30,55–62]
	Glutamine addiction	[63]
	BMSCs	[64]
	BMMSCs	[65]
	CAFs	[11]
	In vitro vs. *in vivo* culture conditions, the latter conducive to oxidative metabolism	[66]
	Nutrient deprivation	[67–69]
	Antitumor chemotherapeutics	[15,24,25,70–76]
	Anti-VEGF mAbs	[67]
	Aurora kinase A inhibitors	[77]
	TKIs	[78–82]
	Serine-threonine kinase inhibitors	[35,83–86]
	PI3K inhibitors	[87]
	HDACis	[88,89]
	Proteasome inhibitors	[26,88,90]
	NAMPT inhibitor	[91]
	Irradiation	[92]

Abbreviations: AIFM2, apoptosis-inducing factor mitochondria associated 2; BMSCs, bone marrow stem cells; BMMSCs, bone marrow mesenchymal stem cell; BRSK1, BR serine/threonine kinase 1; CAFs, cancer-associated fibroblasts; CLPP, caseinolytic protease P; COX6B2, cytochrome c oxidase subunit 6B2; HDACis, histone deacetylase inhibitors; IGF2BP3, insulin-like growth factor-2 mRNA-binding protein 3; KRAS, Kirsten rat sarcoma virus; LRPPRC, leucine-rich pentatricopeptide repeat containing; MCL1, myeloid cell leukemia 1; NAMPT, nicotinamide phosphoribosyltransferase; NRAS, neuroblastoma RAS; PI3K, phosphoinositide 3-kinase; PKM1, pyruvate kinase isoform M1; Rb, retinoblastoma protein; sANK1, small ankyrin 1; SIRT3, NAD-dependent deacetylase sirtuin-3, mitochondrial; SMARCA4, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4; SYK, spleen tyrosine kinase; TKIs, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor.

ibrutinib in myeloid cell leukemia (MCL), with the ETC complex I inhibitor IACS-010759 reducing tumor cell proliferation and tumor growth [100]; to the fms-like tyrosine kinase 3 (FLT3) inhibitor gilteritinib in AML cells [78]; to epidermal growth factor receptor (EGFR)-TKIs in NSCLC cells [79,82]; to mitogen-activated protein kinase (MAPK)

inhibitors in human melanoma cells [34,35]; to BRAF inhibitors in BRAF-mutated melanoma cells [84–86,101]; to the proteasome inhibitor carfilzomib in MM cells [90]; to the NAMPT inhibitor FK866 in TNBC cells (MDA-MB-231) [91]; to an Aurora kinase A inhibitor through inhibition of MYC targets and activation of peroxisome proliferator activated receptor alfa (PPARα) in GBM cells [77]; to the pan-AKT inhibitor uprosertib in CRC cells in response to lactic acidosis [60]; and to the c-MET inhibitor crizotinib in GBM cells [80].

Finally, tumor-associated oxidative metabolism has also been shown to induce resistance against anti-programmed cell death protein 1 (PD-1) immune checkpoint inhibitors [102], with inhibitors of oxidative metabolism being able to restore sensitivity to these drugs [102,103]. It also induced resistance to irradiation upon mechanistic target of rapamycin (mTOR)-mediated inhibition of hexokinase 2 (HK2) and glycolysis [92].

Tumor Type

A factor that may induce upregulation of oxidative metabolism is the tumor type. In fact, it has been claimed that the metabolic profile of tumors depends, among other factors, on the tissue type that originates the tumor [104]. We did not find, however, a convincing association between a given tumor type and upregulated oxidative metabolism. Thus, a predominantly oxidative metabolism has been reported to be associated with many types of solid tumors such as PDAC [68], renal cell cancer (RCC) [105], CRC [106], lung cancer [41], prostate cancer [43], breast cancer [44], cervical cancer [45], cholangiocarcinoma [57], OC [67], melanoma [102], GBM [88], hepatocellular carcinoma (HCC) [49] and neuroblastoma [107]. A similar association has also been found for hematological malignancies such as AML, MM, different types of B-cell non-Hodgkin lymphoma [100,108], T-ALL [37], and chronic myeloid leukemia (CML) [109].

Tumor Stage

Regardless of the tumor type, upregulated oxidative metabolism may preferentially associate with one or more tumor stages such as tumor initiation, tumor cell proliferation and growth migration, and metastatic dissemination, or phenotypic changes like epithelial-mesenchymal transition (EMT) and autophagy [31,110]. Again, no conclusive answer is yet available, but there are some indications that oxidative metabolism may preferentially, although not exclusively, be associated with some of these stages, as we will discuss in the following.

Tumor Initiation

A causative role of oxidative metabolism in tumor initiation has been suggested in a *Drosophila* brain tumor model [111]. These tumors contain a rapidly dividing cancer stem-like cell (CSC) population, derived from neural stem cells. This cell population has an upregulated oxidative metabolism that gives rise to an expanded pool of oxidized NAD required for CSC immortalization, possibly because of its role as co-factor for poly-adenosine diphosphate (ADP) ribosylation and sirtuin-mediated deacetylation, thereby influencing chromatin plasticity, genome stability, and cell fate. Another study suggested that oxidative metabolism might play a crucial role in the initiation of MYC-induced T-ALL in a zebrafish model [112]. In that study, heterozygous inactivation of dihydrolipoamide S-succinyltransferase (DLST), the E2 transferase of the α-ketoglutarate (α-KG) dehydrogenase complex (KGDHC) that converts α-KG to succinyl-CoA in the TCA cycle, delayed tumor onset in zebrafish without detectable effects on fish development. DLST inactivation led to the accumulation of α-KG and a decrease in succinyl-CoA. In addition, oxidative metabolism may also contribute to early tumorigenesis through metabolites (so-called “oncometabolites”) of the TCA cycle, such as succinate, fumarate, and 2-hydroxyglutarate, which undergo a pathological accumulation due to mutations in the TCA cycle enzymes succinate dehydrogenase and fumarate hydratase. A detailed discussion of the role and function of these oncometabolites in tumorigenesis is beyond the scope of this article and the reader is referred to recent literature references (e.g., [113]). Overall, these observations suggest that upregulated oxidative metabolism may play a causative role in the early steps of tumorigenesis. A similar role has also been reported for glycolytic/lactogenic metabolism [6].

CSCs

In addition to the evidence showing that upregulated oxidative metabolism may play a causative role in tumor initiation, there is also considerable evidence for the role of oxidative metabolism in supporting the maintenance of CSCs. The term CSCs, as commonly used, however, encompasses both true tumor-initiating cells as well as tumor cells that undergo phenotypic changes (e.g., EMT) allowing them to resist stressors from the TME and to give rise to a new wave of tumor cell offspring [114,115]. Moreover, CSCs, whatever their origin, are, per se, a heterogeneous cell population that includes a pool of quiescent cells and a pool of proliferating cells [116]. With this information in mind, we now discuss some examples of the role of oxidative metabolism in CSC biology.

CSCs from several solid and hematological tumors [117] (Zhao Z, *et al*. 2022) have been shown to rely on upregulated oxidative metabolism for their survival [117]: cholangiocarcinoma [118], gastric cancer [119], breast cancer [33,39], small cell lung cancer (SCLC) [120], PDAC [121,122], CRC [53,123], OC [124], CML [125,126], B cell-ALL [127], and AML [42,54,71,128]. In some cases, it was shown that CSCs utilized predominantly oxidative metabolism, whereas the bulk of cancer cells utilized lactogenic metabolism [129]. In another case, both oxidative and

lactogenic metabolism were crucially involved in CSC biology [130]. It should be noted, however, that in other cases, CSC biology was shown to rely predominantly on lactogenic metabolism [6,131,132]. In the following (see section 7), we will discuss some possibilities to explain these apparently contradictory results.

Quiescent Tumor Cells

Several reports suggest that quiescent tumor cells preferentially use oxidative metabolism for their maintenance [133,134], in a manner similar to quiescent non-tumor cells [135]. This has been shown for several tumor types like melanoma ([59,85,136], CRC [137], PDAC [122,138], GBM [139,140], and CML [141]). Some CSC populations have also been shown to be relatively inactive from a metabolic point of view and rely mainly on oxidative metabolism to meet their energy requirements. This has been shown for CSC in the SCLC cell line H446 [120] and with primary specimens derived from AML patients [128].

Proliferating Tumor Cells

Most available evidence suggests that tumor cell proliferation and primary tumor growth rely predominantly on lactogenic metabolism [1,2,121,132]. In several instances, however, oxidative metabolism was the main metabolic pathway supporting tumor cell proliferation and growth (e.g., [24,36,39,40,50,61,84,142–146]). In some cases, this has been shown by inhibiting the activity of inducers of oxidative metabolism. Thus, MM cells showed impaired proliferation upon treatment with an inhibitor of the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) [147]; TNBC, breast CSCs, NSCLC, mantle-cell lymphoma, PDAC and neuroblastoma cells showed impaired proliferation and tumor growth in response to different anti-mitochondrial drugs [22,68,79,100,107,148–152]; osteosarcoma cells lacking mitochondrial ETC complex III showed inhibition of primary tumor growth [153]; and EGFR-TKI-resistant lung cancer cells which were addicted to glutamine as a carbon source for TCA cycle-intermediates showed inhibition of proliferation upon addition of a glutaminase inhibitor [154].

On the other hand, there is also direct experimental evidence showing that oxidative metabolism does not induce the proliferation of tumor cells, or even inhibit it. Thus, lactate reduced the proliferation and migration of uveal melanoma cells while inducing metabolic reprogramming towards oxidative metabolism [59]. In PDAC cells, induction of oxidative metabolism promoted metastasis formation but not tumor cell proliferation [155]. Similarly, silencing of PGC-1α in cancer cells reduced their metastatic potential without affecting tumor cell proliferation and primary tumor growth [156]. Finally, the ETC complex I inhibitor metformin at low doses inhibited ovarian CSCs without affecting bulk tumor cell proliferation [157].

Metastasis Formation

Tumor cell invasion, migration, and dissemination lead to the formation of metastases which represent the main cause of death in cancer patients. In the previous section, we cited studies showing that metastasis formation is supported by a predominantly oxidative metabolism. Thus, using metastasis-derived, patient-derived xenografts and isogenic cell lines, it has been shown that a fraction of estrogen receptor-positive breast cancers relies mainly on oxidative metabolism [158]. Similar results have been reported for breast cancer [39,156,159,160], HCC [49], CRC [123], epithelial OC [50], PDAC [87,155], melanoma [87,161], GBM [87], RCC [105]. Interestingly, in some cases, metastasis formation was found to be more dependent on oxidative metabolism than was the corresponding primary tumor [155,159], whereas others observed the opposite [66]. It should be noted, however, that metastasis formation is a complex process that encompasses several successive steps, i.e., invasion and migration, intravasation, extravasation, deposition, and proliferation of metastatic cells. It appears likely that tumor cells may utilize different metabolic pathways during their journey from primary sites to sites of metastasis formation, which may help explain contradictory results that have been published on this point over the years, some of which have shown that metastasis formation relies mainly on lactogenic metabolism (e.g., [162–166]). We will come back to this point in a later section (section 7).

Epithelial-Mesenchymal Transition (EMT) and Autophagy

EMT and autophagy are two different aspects of tumor cell response to intracellular or extracellular stressors [114,167,168]. In EMT, tumor cells tend to escape from their site of primary tumor growth and settle down in other, even distant organs, in order to give rise to metastases. In autophagy, tumor cells switch from anabolic to catabolic metabolism in order to survive as long as the stressor persists. In spite of these fundamental differences, EMT and autophagy undergo extensive cross-talk and can even coexist in the same tumor cells [168]. Most available evidence suggests that EMT is associated with a predominantly lactogenic metabolism [169–171], while autophagy relies mainly on oxidative metabolism [138,141,171,172]. In fact, these associations appear reasonable in view of the different responses and metabolic needs of tumor cells undergoing EMT or autophagy. Thus, EMT requires a quick metabolic response in order to meet the energetic needs that the phenotypic change and functional consequences (e.g., invasion and migration) require, and that is best matched by an upregulation of lactogenic metabolism for the reasons we have stated in the introduction. On the other hand, the metabolic needs of non-proliferating, autophagic cells that are in a catabolic state may benefit more from oxidative metabolism. Interestingly, autophagic tumor cells represent a phenotype that has been reported to overlap, at least

in part, with two other phenotypic states and functionalities that we have discussed before, i.e., quiescence and CSCs [173–176]. It would, however, go beyond the scope of the present article to discuss this topic in greater detail.

Although the bulk of available evidence suggests the association between EMT and lactogenic metabolism on the one hand, and between autophagy and oxidative metabolism on the other hand, in some cases the boundaries appear to be less defined. Thus, using human breast epithelial cells engineered to express a mesenchymal phenotype on a non-tumorigenic or tumorigenic (H-RasV12) background, it was shown that both cell types showed elevated oxidative metabolism using lactogenic metabolism end-products such as lactate, or β-oxidation and TCA cycle substrates [177]. Moreover, TGF-β, the prototypic EMT inducer, has been shown to stimulate both lactogenic as well as oxidative metabolism in cells undergoing EMT [178].

Metabolic Requirements that Drive Upregulation of Oxidative Metabolism in Tumor Cells

So far, we have discussed how tumor cell-intrinsic and -extrinsic stimuli promote the upregulation of oxidative metabolism in tumor cells. We will now consider some metabolic requirements of tumor cells that lead to the upregulation of oxidative metabolism (Table 2, Ref. [26,28–30,36,55–62,73,77,82,89,92,94,95,111,151,153,172,179–186]).

Upregulation of oxidative metabolism occurs when the alternative energy-generating pathway, i.e., lactogenic metabolism, is obstructed. We have already discussed some examples that highlight this occurrence. Thus, Aurora kinase A inhibition led to an upregulation of oxidative metabolism that was mediated by enhanced FAO and concomitant suppression of lactogenic metabolism [77]. Inhibition of AKT and extracellular signal-regulated kinase (ERK) 1/2 signaling in NSCLC cells caused suppression of lactogenic metabolism and concomitant upregulation of OXPHOS [82]. HDAC inhibition suppressed lactogenic metabolism in GBM cells and upregulated oxidative metabolism driven by increased FAO [89]. Downregulation of hypoxia-inducible factor-1alpha (HIF-1α) in OC cells inhibited lactogenic metabolism and upregulated OXPHOS [179]. Inhibition of LDHA activity in tumor cells stimulated oxidative metabolism [180]. A shift from lactogenic to oxidative metabolism in tumor cells was observed upon inhibition of pyruvate dehydrogenase kinase (PDK) activity [181]. Cell lines from different tumor types (breast, colon, glioblastoma) showed relocation of mTOR to the outer membrane of mitochondria where it bound to HK2 [92]. This caused dissociation of HK2 from mitochondria and inhibited its activity, thereby leading to decreased lactate production and upregulation of oxidative metabolism. Whereas obstruction of lactogenic metabolism leading to upregulation of oxidative metabolism has been relatively neglected over the years, the opposite pathway, i.e., inhibition of oxidative metabolism leading to upregulation of lactogenic metabolism, is a well-known side effect of therapy with metformin and other biguanides (e.g., phenformin). Their mechanism of action depends on the inhibition of ETC complex I leading to inhibition of OXPHOS and, consequently, to upregulation of lactogenic metabolism with overproduction of lactate resulting in systemic lactic acidosis [187–189].

It may appear paradoxical, but the second metabolic occurrence that leads to the upregulation of oxidative metabolism in tumor cells is the upregulation of lactogenic metabolism itself, leading to lactic acidosis and increased lactate levels in the tumor microenvironment. We have already mentioned several cases showing that lactic acidosis and lactate itself [28,30,55–58,60–62] can induce metabolic reprogramming towards oxidative metabolism [29,59]. Interestingly, it has recently been shown that lactate stimulates ETC activity to increase OXPHOS and, consequently, mitochondrial ATP production which then suppresses glycolysis [182]. Taken together, these observations suggest that oxidative metabolism becomes upregulated either when lactogenic metabolism is inhibited “too much” or when it is stimulated “too much”. This suggests that a finely tuned equilibrium exists between these two metabolic pathways and, although the mechanisms that underlie this reciprocal tuning are beginning to be unveiled [182], we are still far from having a complete picture.

Oxidative metabolism also becomes upregulated due to peculiar metabolic requirements of the tumor cells during tumor development. An increased demand for ATP molecules represents such a requirement. Thus, it has been shown that upregulated oxidative metabolism boosts ATP production to support ABC-mediated efflux of chemotherapeutics out of tumor cells [95]. Mitochondrial ATP production was also required to support the activity of mitochondria-localized drug efflux pumps in doxorubicin-resistant breast cancer cells [183]. Upregulated oxidative metabolism leading to greatly increased ATP production was also observed in photodynamic therapy-induced chemoresistance in cancer cell lines [94]. Similarly, upregulated oxidative metabolism was required to support ABCB1 drug efflux in the presence of doxorubicin [73]. In this case, upregulated ABCB1 itself caused OXPHOS upregulation. Although a direct cause was not demonstrated, it is reasonable to assume that drug efflux also occurred as a result of increased ATP production in this case. Increased ATP production, however, does not only support ABC activity. Thus, homologous recombination-defective cancers have been shown to utilize oxidative metabolism to supply ATP (and oxidized NAD) for poly (ADP-ribose) polymerase-dependent DNA repair mechanisms [184]. This was accompanied by a decline in lactogenic metabolism suggesting that metabolic plasticity can allow rapid adaptation of cancer cells to different circum-

Table 2. Metabolic causes that lead to upregulation of oxidative metabolism in tumor cells.

Main Causes	Examples	References
Inhibition of lactogenic metabolism	In response to:	
	Irradiation, relocation of mTOR to OMM where it induced inhibition of HK2	[92]
	Aurora kinase inhibition	[77]
	Inhibition of AKT and ERK1/2 signaling	[82]
	HDAC inhibition	[89]
	Downregulation of HIF-1α	[179]
	Inhibition of LDHA or PDK	[180,181]
Upregulation of lactogenic metabolism	In response to:	
	Lactic acidosis	[28,30,55–58,60–62]
	Lactate	[29,59,182]
Increased demand for ATP	Increased production of ATP to support efflux of chemotherapeutics out of tumor cells	[73,94,95,183]
	Increased supply of ATP for poly (ADP-ribose) polymerase-dependent DNA repair mechanisms in HRD tumors	[184]
Increased demand for metabolic outputs other than ATP	Fueling of PPP and generation of ROS at Qo site of ETC complex III for anchorage-independent growth	[36]
	Increased ubiquinol activation to promote the functioning of ETC complexes I and II in order to regenerate oxidized NAD and FAD required for the TCA cycle and pyrimidine synthesis	[153]
	To provide electron acceptors for aspartate synthesis through the respiratory chain	[185,186]
	To promote asparagine synthesis through ETC complexes in order to support mTORC1 activity and its tumor-promoting effects	[151]
	To regenerate oxidized NAD required for immortalization of neural stem cells in a *Drosophila* tumor model	[111]
	To increase NADPH production needed to reduce proteotoxic stress	[26]
	To produce enough succinate in order to support the survival of leukemia cells	[172]

Abbreviations: ADP, adenosine diphosphate; ATP, adenosine triphosphate; ERK, extracellular signal-regulated kinase; ETC, electron transport chain; FAD, flavin adenine dinucleotide; HDAC, histone deacetylase; HIF-1α, hypoxia-inducible factor-1alpha; HK2, hexokinase 2; HRD, homologous recombination-defective; LDHA, lactate dehydrogenase A; mTOR, mechanistic target of rapamycin; NAD, nicotinamide adenine dinucleotide; NADPH, reduced nicotinamide adenine dinucleotide phosphate; OMM, outer mitochondrial membrane; PDK, pyruvate dehydrogenase kinase; PPP, pentose phosphate pathway; ROS, reactive oxygen species; TCA, tricarboxylic acid.

stances that may occur during tumorigenesis. Another article reported a discrepancy between the energetic needs of tumor cells grown *in vitro* or *in vivo* as lung tumor xenografts. When grown *in vitro*, tumor cells showed overexpression of glycolytic genes and increased sensitivity for glycolytic inhibition while, *in vivo*, down-regulation of glycolytic mechanisms and increased respiratory chain function and ATP production were required for primary tumor growth [66].

On the other hand, there are reports that argue against any tumor-promoting or -supporting effect of increased mitochondrial ATP production and even suggest a cytotoxic effect. Thus, in AML cells acute enhancement of ATP production was highly cytotoxic to leukemic blasts, suggesting that the requirement for mitochondria in AML was unrelated to ATP production but, rather, was required to support other aspects of anabolic growth [145]. In this regard, it should be recalled that in nonproliferating cells oxidative metabolism maximizes ATP production, whereas it serves mainly as an important source of biosynthetic precursors in proliferating cells [190].

As to these ATP-unrelated effects of tumor cell-associated oxidative metabolism, it has been reported that KRAS-induced, anchorage-independent growth of tumor cells depends on feeding the PPP pathway and the generation of ROS at the Qo site of the ETC complex III [36]. Later, the same group showed that ETC complex III was necessary for tumor growth through ubiquinol oxidation which, in turn, was required for the function of ETC complexes I and II which regenerate mitochondrially oxidized NAD and FAD for the TCA cycle and pyrimidine synthesis [153]. Other authors showed that a major function of oxidative metabolism in proliferating tumor cells and immortalized fibroblasts was to provide electron acceptors for aspartate synthesis through the respiratory chain [185,186]. Moreover, in a panel of tumor cell lines oxidative metabolism promoted asparagine synthesis through the ETC complexes. Asparagine, in turn, supported mTORC1 activity and the tumor-promoting effects linked to it [151]. As already discussed, oxidative metabolism was also required for the immortalization of neural stem cells in a *Drosophila* tumor model [111]. Blocking OXPHOS pre-

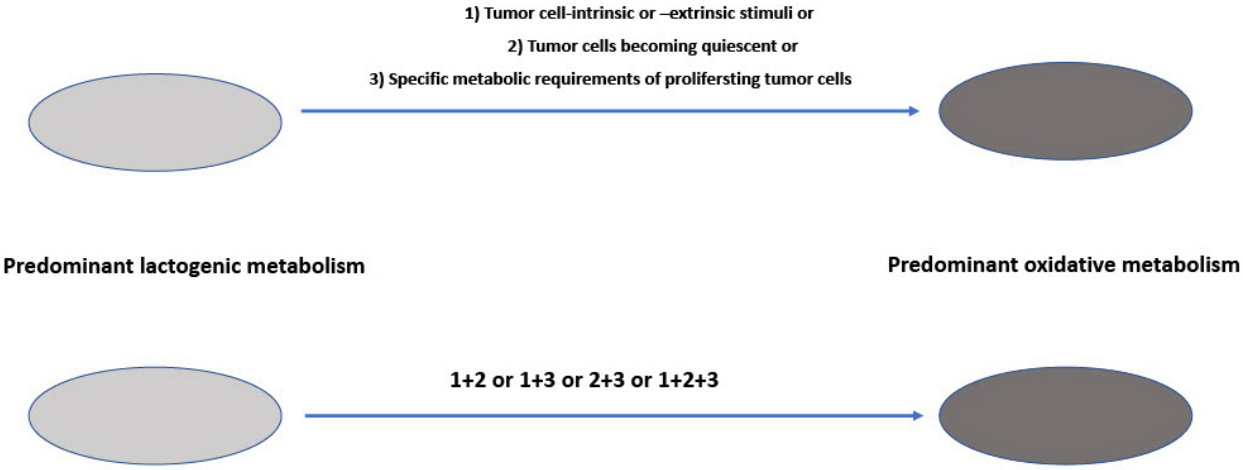

Fig. 2. Modes of upregulation of oxidative metabolism in tumor cells. The upper part shows that tumor cells can undergo reprogramming towards oxidative metabolism in response to individual factors (depicted as 1, 2 or 3) if these factors transmit a signal that is strong enough to induce reprogramming alone. The lower part depicts the situation where each of the individual factors is not strong enough but becomes so if they act contemporarily on the tumor cell (depicted as 1+2 or 1+3 or 2+3 or 1+2+3). The figure was created with PowerPoint 2021.

vented tumorigenesis through impaired oxidized NAD regeneration. In nutrition-deprived tumor cells OXPHOS was upregulated and this, in turn, inhibited glycolytic metabolism through oxidized NAD-dependent SIRT1 activation [69]. Proteasome inhibitor-resistant MM cells increased reduced NADP production through overexpression of malate dehydrogenase and PPP enzymes in order to reduce proteotoxic stress [26]. Succinate acted as a tumor cell survival factor in a leukemia model [112] where inhibition of DLST disrupted the TCA cycle and induced apoptosis in T-ALL cell lines. The addition of succinate rescued viability in these cells. It was shown that, during quiescence, in non-tumor cells, OXPHOS constitutively generated low levels of endogenous ROS that induced autophagy via attenuation of ATG4B activity, and this provided resistance and survival in response to acute, high-level ROS insult [172].

In these sections, we have discussed several factors which can induce upregulation of oxidative metabolism in tumor cells. We suggest that each of these factors has the potential to upregulate oxidative metabolism in its own right if the signal that it transmits is strong enough. We propose, however, that in most cases it is the simultaneous occurrence of two or more of these factors that is required to achieve a signal strength conducive to the upregulation of oxidative metabolism. Fig. 2 gives a representation of the model that we propose. We believe that an additional advantage of this model is that it allows for fine-tuning of the level of upregulation of oxidative metabolism, as may be required at a given time point of tumor growth and dissemination.

Prognostic Implications of Upregulated Oxidative Metabolism in Tumor Cells

One way to estimate the consequences of upregulated oxidative metabolism is to assess its impact on the prognosis of tumor patients. Several articles have investigated this aspect and have reached the conclusion that upregulated oxidative metabolism has a negative impact on tumor prognosis [191]. Thus, cholangiocarcinoma patients with upregulated oxidative metabolism had shorter overall survival and progression-free survival [118]. Similar results were reported for estrogen-receptor-positive breast cancer patients [158]. Analysis of samples from patients undergoing immunotherapy with immune checkpoint inhibitors showed that upregulated oxidative metabolism, but not lactogenic metabolism, was associated with tumor progression on anti-PD-1 therapy [19]. AML patients with high OXPHOS levels were found to have a poor prognosis [192]. Upregulated oxidative metabolism in high-risk neuroblastoma patients was associated with poor treatment outcomes and aggressive disease [107]. Mitochondrial elongation and upregulated OXPHOS were associated with poor prognosis in HCC patients [69]. In addition, overexpression of OXPHOS genes was associated with poor prognosis in MM patients [147].

The Mechanism of Tumor Cells Upregulating Oxidative Metabolism

Throughout this article, we have discussed the factors, whether tumor cell-intrinsic or -extrinsic, that lead to the upregulation of oxidative metabolism. In this section, we discuss how such upregulation occurs from a mechanistic point of view.

Upregulation of oxidative metabolism is the consequence of the upregulation of the enzymes that are part of the pathways of oxidative metabolism, i.e., the TCA cycle and OXPHOS. Thus, upregulation of TCA cycle enzymes [88,102,127] and/or OXPHOS components [18,27,38,48,64,65,67,69,82,84,90,138,161] has been shown to lead to enhanced oxygen consumption and increased respiratory capacity. With respect to individual enzymes, increased oxidative metabolism was associated with increased expression of the DLST component of the KGDHC complex [193], of PKM1, a glycolytic enzyme that promotes oxidative metabolism in tumor cells [52,53], of the pyruvate dehydrogenase (PDH) complex [88,102,127], a gatekeeper enzyme of the TCA cycle, of complex I of the ETC [20,160,194], of complexes II and IV of the ETC [160], and of OXPHOS subunits [48]. Increased expression of these enzymes can be due to increased synthesis of mitochondrial proteins and OXPHOS subunits [82,85,96]. Upregulation of oxidative metabolism is also accompanied by morphological changes in mitochondria, i.e., the site where oxidative metabolism occurs. Thus, increased mitochondrial biogenesis [49,74,101,195], increased mitochondrial mass and mitochondrial DNA content [15,61,90], and increased mitochondrial elongation facilitating cristae formation and assembly of respiratory complexes [69,72], and mitochondrial hyperfusion [58] have been observed concurrently with upregulated oxidative metabolism. The changes affecting mitochondria and oxidative metabolism enzymes are accompanied by increased utilization of the metabolic substrates of oxidative metabolism. This has been demonstrated, e.g., for lactate, β-oxidation substrates, and TCA cycle substrates such as succinate [80,83,89,177,196] and glutamine [27,76,84,90,154].

Increased synthesis of mitochondrial proteins and/or OXPHOS subunits, in turn, [82,85,96] are the result of the activation or overexpression of transcription factors (TF) or TF coactivators involved in their transcription, or of epigenetic modifiers (e.g., peroxisome proliferator-activated receptors, PGC-1α, MYC, SIRTs, etc.) [18,21,32,35,46,49,50,58,61,62,77,80,85,86,89,93,101,118,121,147,156,196,197]. Alternatively, the down-regulation of negative regulators of mitochondrial metabolism (e.g., methylation-controlled J protein, MCJ) can also lead to the upregulation of oxidative metabolism [95].

Conclusions

In this article, we have discussed the mechanisms leading to the upregulation of oxidative metabolism in tumor cells, and its biological consequences. While certain aspects of this regulation are yet to be fully understood, established knowledge provides a foundation for further investigation.

As already reiterated many times in the literature, proliferating tumor cells rely mainly on lactogenic metabolism to meet their energetic and biosynthetic demands. This can be considered as the default pathway for proliferating tumor cells. On the other hand, quiescent tumor cells rely predominantly on oxidative metabolism. The dichotomy between tumor cell proliferation-associated lactogenic metabolism and quiescence-associated oxidative metabolism may also explain the contradictory results that have been reported for the metabolism of CSCs. In fact, and as already discussed, CSCs represent a heterogeneous population of cells encompassing both quiescent and proliferating cells. It appears reasonable to assume that the balance between these two states may vary according to the need to replenish, or not, the pool of proliferating tumor cells, and this may imply a predominance of lactogenic or oxidative metabolism, respectively. A similar explanation may apply also to the contradictory results that have been reported for metastasis formation. As already discussed, the process of tumor cell dissemination and metastasis formation is complex and multistep and may rely predominantly on one metabolic pathway or the other, depending on the step that is being traversed at a given time point.

Let us now consider the metabolic requirements of proliferating tumor cells in primary tumors. As already mentioned, in this situation, the upregulated lactogenic metabolism can be considered as the default pathway to meet energy and other metabolic requirements of tumor cells. In certain situations, however, oxidative metabolism becomes upregulated because its output(s) appear more suitable to support tumor cell proliferation and tumor growth than lactogenic metabolism. Thus, upregulated oxidative metabolism may boost ATP production required to support the activity of ATP-dependent drug efflux pumps. Moreover, increased ATP and oxidized NAD production may be required to support DNA repair mechanisms. In other settings, metabolic outputs other than ATP may be required to support tumor cell proliferation and tumor growth. Thus, upregulated oxidative metabolism is required for the regeneration of oxidized NAD and FAD used in the TCA cycle and for pyrimidine synthesis [153], to support aspartate or asparagine synthesis [151,185,186], to regenerate oxidized NAD for the immortalization of neural stem cells [111] or SIRT1 activation [69], to upregulate succinate production required for the survival of leukemic cells [112], and to generate low levels of ROS which promotes cell survival and resistance [172].

In a previous section, we established that no convincing association between a given tumor type and upregulated oxidative metabolism has been observed, although the tissue type that originates the tumor may influence the metabolic phenotype [104]. It should be added, however, that a careful analysis of the metabolic phenotype of individual tumor types and appropriate tumor subtypes, is still lacking. This is an area of considerable interest for

future research because of the obvious therapeutic consequences that a more comprehensive understanding of this issue would have.

Another important question that arises is whether, on the basis of the information that we have discussed so far, we can draw any conclusion regarding the possibility of inhibiting tumor growth and dissemination by harnessing the metabolic dependencies that we have described. In our eyes, the answer is probably no, at least in the short term, for several reasons. First, the metabolic plasticity of tumor cells with the potential to shift from lactogenic to oxidative metabolism and vice versa is very significant and, for the reasons that we have described, the shift is never absolute, since one predominates over the other but both coexist in the same tumor cells. On this basis, it is reasonable to predict, and as it has been shown experimentally (see a previous section), that upon pharmacological inhibition of one of the two metabolic pathways (lactogenic or oxidative metabolism), the other becomes upregulated in order to support tumor growth. One possible way out of this dilemma is to block both lactogenic and oxidative metabolism in order to inhibit overall ATP production and/or other metabolic outputs. Although there are preclinical results that suggest the feasibility of this approach [88,130,198], we should consider that the clinical development of a novel OXPHOS inhibitor has been recently discontinued because of unacceptable side effects [199]. Moreover, clinical trials performed so far with an established ETC complex I inhibitor, metformin, have yielded disappointing results in terms of efficacy [200]. On this basis, it seems reasonable to expect that pharmacological approaches aimed at inhibiting both lactogenic as well as oxidative metabolism may be accompanied by intolerable toxicities or lack of efficacy. One possibility to bypass such a limitation would be to take advantage of active targeting approaches [201], i.e., targeting the compound of interest, whether an inhibitor of lactogenic or oxidative metabolism, only to tumor cells, thereby limiting or avoiding undesired side effects. There are several active targeting approaches that have been described over the last decades, some of which have been successfully applied for the generation of actively targeted compounds that are now in current clinical use like, for example, antibody-drug conjugates (ADC) [202]. Thus, one possibility is to target inhibitors of oxidative metabolism to cell surface receptors that are preferentially or exclusively expressed on the surface of tumor cells like CD20 or HER2, to name just two of the most successful tumor targets that have been identified. Given the relative or absolute tumor specificity of such an approach, one can also consider the possibility of combining the delivery of inhibitors of oxidative metabolism in combination with inhibitors of glycolysis. This would prevent the possibility of bypassing the inhibition of one of the two main energy-generating metabolic pathways through activation of the other pathway without being accompanied by unacceptable side effects. An approach of this kind could also be exploited to complement and improve current antitumor approaches [203]. Active targeting of metabolic inhibitors is certainly an avenue that warrants investigation, but it remains to be demonstrated that it is at least as efficacious as other active targeting approaches like, for example, ADCs [202] that we have previously referred to and which are now established components of the available antitumor armamentarium. We believe that this approach is worth being pursued but we should not expect results amenable to therapeutic application in the short term.

Availability of Data and Materials

Not applicable.

Author Contributions

FM and CR have made substantial contribution to the conception and design, acquisition of the data, and analysis and interpretation of the data. Both authors contributed to the drafting and critical revision of the manuscript. Both authors have given final approval of the version to be published and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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