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### Abstract

Metabolic rearrangements are essential to satisfy the different requirements of cancer cells during tumorigenesis and recent studies highlighted a role for such metabolic reprogramming in response and adaptation to therapies. However, therapy-resistant experimental models have been described to be either glycolysis-dependent or OXPHOS-addicted. Here we discuss the recent literature on metabolic reprogramming of cancer in therapy resistance with a plausible explanation of the observed differences which collectively indicate that dis-regulated metabolic pathways could be considered as potential therapeutic target in tumors resistant to conventional therapy.

**Keywords** Metabolic reprogramming; Warburg metabolism; OXPHOS; therapy resistance

**Taxonomy** Experimental Oncology, Clinical Oncology, Molecular Oncology

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1 **Linking metabolic reprogramming to therapy resistance in cancer**

2

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1 **Abstract**

2 Metabolic rearrangements are essential to satisfy the different requirements of cancer cells  
3 during tumorigenesis and recent studies highlighted a role for such metabolic  
4 reprogramming in response and adaptation to therapies. However, therapy-resistant  
5 experimental models have been described to be either glycolysis-dependent or OXPHOS-  
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7 therapy resistance with a plausible explanation of the observed differences which  
8 collectively indicate that dis-regulated metabolic pathways could be considered as  
9 potential therapeutic target in tumors resistant to conventional therapy.

10

## 1 **Introduction**

2 Preventing or bypassing drug resistance is arguably the most important unmet medical  
3 need in cancer management. Targeted therapies have been used effectively both as  
4 monotherapy and/or in combination with chemotherapy in the vast majority of tumors.  
5 However, resistance still limits their clinical benefit and patients experience relapse that  
6 includes distant metastases caused by resistant clones unaffected by the selective  
7 pressure of the therapy and able to repopulate the tumor. Identification of biomarker-  
8 defined patient populations that will most likely respond to the drugs is therefore essential  
9 (i) to maximize benefit from targeted therapies and (ii) to minimize exposure of patients to  
10 unnecessary treatments that have important side-effects and are expensive.

11 Metabolic deregulation is an established hallmark of cancer. It is well documented that  
12 most cancer cells enhance glucose and glutamine consumption to satisfy their energy  
13 demand and biosynthesis requirements for rapid proliferation. Importantly, Warburg  
14 reported that, even in the presence of oxygen, cancer cells show increased glycolysis  
15 using only a small fraction of glucose for oxidative phosphorylation (OXPHOS). However,  
16 whether such metabolic deregulation towards a Warburg-like metabolism is a requisite of  
17 the population of cancer cells responsible for therapy adaptation, residual disease and  
18 ultimately tumor relapse, remains a matter of debate.

19 Importantly, most studies that link metabolism and therapy resistance are correlative and  
20 did not directly prove that metabolic reprogramming is causative and not a mere bystander  
21 effect of signaling and proliferative inputs that characterize resistant cancer cells. On the  
22 other hand, resistant cell subpopulations in different types of tumors have been described  
23 to be either Warburg-like or OXPHOS-addicted, with plausible explanations as to which  
24 metabolic phenotype could be advantageous during tumor development and adaptation to  
25 therapy. The aim of the current perspective is to discuss the emerging literature on

1 metabolic reprogramming in therapy response and resistance and to give a tentative  
2 answer to such *conundrum*.

3 We reviewed recent studies on this topic, which collectively suggest that metabolic  
4 reprogramming that resistant cancer cells undergo is profoundly influenced by the type of  
5 therapy. Crucially, we speculate that therapy could have an active role in selecting  
6 resistant clones and, depending on the mechanisms of action, drugs could confer to the  
7 cancer cells a high degree of plasticity making them extremely skillful in rewiring their  
8 metabolic network. For the sake of completeness, it is well established that cancer cells  
9 can catabolize nutrients other than glucose for energy production and anabolic purposes.  
10 However, the current perspective focuses exclusively on central carbon metabolism in  
11 therapy resistance.

12

### 13 **Chemotherapy resistance**

14 Chemotherapy acts by interfering with cancer cells proliferation at different phases of cell  
15 division. Since cell proliferation occurs also in certain normal tissues, side effects during  
16 chemotherapy are common. Several chemotherapy resistance mechanisms have been  
17 described and can generally be divided into genetic, i.e. gene mutation or amplification  
18 that renders the drugs ineffective on a particular subpopulation of cancer cells [1], and  
19 non-genetic, in which cancer cells may find a way to bypass the blockade induced by the  
20 drug and/or decrease the amount of drug inside the cell by reducing its intracellular  
21 transport or by pumping the drug out via multidrug resistance protein transporters [2].  
22 From a metabolic point of view, it is established that a highly proliferative tumor relies on  
23 aerobic glycolysis to sustain a fast growth rate [3]. This is one of the reasons why  
24 chemotherapy becomes selective for cancer cells. Many studies, initially performed in  
25 established cancer cell lines, showed that resistant cells are characterized by aerobic  
26 glycolysis and that lactate levels, as by-products of glycolysis, are enhanced in drug-

1 resistant or metastatic cancers, which implies that the Warburg effect in these cancers  
2 may reflect metabolic adaptations associated with development of resistance to  
3 chemotherapy [4-6]. Nevertheless, due to the toxic effects on highly proliferating cells  
4 exerted by chemotherapy, it is conceivable that a cancer cell has to reduce its proliferation  
5 speed and switch to OXPHOS metabolism, which is characterized by a significantly lower  
6 glucose demand rate but constitutes a more efficient source for energy generation.  
7 Therefore, the emerging idea is that chemotherapy induces a selective pressure,  
8 promoting emergence of a subpopulation of cancer cells capable of surviving in the  
9 presence of the drug, possibly by efficiently generating the ATP necessary for pumping the  
10 drug out of the cell, slowing down the cell cycle with an increase in the population at the  
11 G0 phase in order to avoid cell death. Indeed, several recent studies have shown that  
12 chemotherapy-resistant cancer cells become OXPHOS-dependent [7-11] . Additionally,  
13 increased ATP levels and lower proliferation rate of cancer cells are positively correlated  
14 with chemo-resistance [12].

15  
16 Several studies pointed out that cancer stem cells (CSC) are responsible for therapy  
17 resistance and tumor relapse. Understanding CSC metabolism could therefore offer the  
18 possibility to target such aggressive subpopulations by interfering with their metabolic  
19 features. As recently reviewed by Sancho and co-workers [13], contradictory results  
20 described the CSC metabolic phenotype as glycolytic or OXPHOS-addicted not only in  
21 various tumor types, but also within individual cancer types. In any case, it is conceivable  
22 that OXPHOS dependency could confer a selective advantage to CSCs in the context of  
23 specific tumor microenvironments. Indeed, CSCs could uptake lactate and other carbon  
24 sources secreted by more differentiated cancer cells or by stromal cells that preferentially  
25 undergoes Warburg-like metabolism [14-16]. Despite the fact that the theoretical rationale  
26 of this hypothesis seems to be flawless, most of the data provided on chemotherapy-

1 resistant specimens revealed an increase in glycolytic-related markers in the resistant  
2 patients' cohort [6, 17-19]. A possible explanation could be that few persistent cancer cells  
3 that survived initial drug selection and are undetectable by current diagnostic approaches,  
4 may have already switched to a fast-growing mode once clinical relapse is detectable, and  
5 glycolytic transit amplifying cancer cells may actually account for the majority of the tumor  
6 bulk at this stage (Figure 1).

7

### 8 **Endocrine therapy resistance**

9 Endocrine therapy is the standard of care for breast cancer in which estrogen receptor  
10 (ER) is expressed and controls cancer growth and survival. Such therapy acts by  
11 interfering with ER signaling either by antagonizing binding of E2 to the ER (e.g.,  
12 tamoxifen), promoting ER degradation (e.g., fulvestrant), or blocking E2 biosynthesis  
13 (aromatase inhibitors, AI). However, resistance limits its clinical efficacy. The mechanisms  
14 of such resistance differ substantially to that described for chemotherapeutic agents since  
15 the role of hormones in adult tissue, despite being fundamental, impacts only on certain  
16 tissues. Although genetic events have been reported to concur to therapy resistance [20,  
17 21], the majority of the resistant events are caused by activation of ER signaling  
18 independently of estrogen binding [22]. Such signaling rewiring is paralleled by metabolic  
19 reprogramming of the resistant cells. It has been shown that tamoxifen-resistant cells are  
20 characterized by Hypoxia-Inducible Factor-1 $\alpha$  (HIF-1 $\alpha$ ) hyper-activation via modulation of  
21 Akt/mTOR, resulting in enhanced aerobic glycolysis and a Warburg-like metabolism.  
22 Importantly, impairing glycolysis restores tamoxifen sensitivity in drug-resistant cells,  
23 suggesting that metabolic reprogramming is not merely a consequence of signaling  
24 rewiring [23]. Moreover, a different study reported that when tamoxifen-sensitive cells are  
25 cultured in the presence of fibroblasts, a metabolic symbiosis is established, impacting on  
26 drug response. Indeed, it has been proposed that while cancer associated fibroblasts are

1 undergoing a Warburg-like metabolism, secreting lactate into the media, cancer cells are  
2 able to uptake such carbon sources, thus switching to OXPHOS, and this is sufficient to  
3 confer tamoxifen resistance [24]. However, such interactions also generate a growth  
4 factors/cytokines crosstalk between the cell populations which is difficult to ignore when  
5 analyzing the resistance mechanisms and makes it difficult to draw a definitive conclusion  
6 on metabolic reprogramming [25]. What seems plausible in endocrine therapy resistance  
7 comes from recent studies where metabolic reprogramming of resistant cells shows high  
8 degree of plasticity. Accordingly to Bacci and co-workers, although AI resistant cells  
9 undergo a typical Warburg-like metabolism characterized by enhanced basal glucose  
10 uptake, glycolysis targeting in such cells is ineffective [18]. Indeed, resistant cells were  
11 able to shift *ad hoc* between Warburg and OXPHOS metabolism, a phenomenon directed  
12 by the microRNA-155 (Figure 2). Glycolytic parameters were found to correlate with  
13 endocrine therapy response and microRNA-155 levels display prognostic value [18].  
14 Sansone and co-workers' study has further supported this "chameleonic" metabolic  
15 behavior of endocrine therapy resistant cells [26]. Crucially, they reported that endocrine  
16 therapy selected a metabolic dormant cancer stem cell-like subpopulation characterized by  
17 the loss of mitochondrial bioenergetics. Importantly, the exit from this metabolic dormancy  
18 is orchestrated by IL6 signaling that impacts on ER expression and function and  
19 culminates in reacquisition of glycolytic and OXPHOS metabolic activity. Taken together,  
20 these data highlight the importance of metabolic adaptability of cancer cells for endocrine  
21 therapy resistance and suggest that targeting such metabolic plasticity could be a novel  
22 approach to combat and/or delay disease recurrence.

23

#### 24 **Antiangiogenic therapy resistance**

25 It is established that administration of antiangiogenic therapy causes a rise in hypoxia in  
26 the targeted tissues and subsequent HIF1 $\alpha$ -mediated upregulation of glycolysis genes,

1 including glucose transporter 1 (GLUT1), lactate dehydrogenase A (LDHA),  
2 monocarboxylate transporter 4 (MCT4) [27, 28]. More recent data further support the  
3 hypothesis that antiangiogenic drugs might rewire tumor metabolism, including both  
4 studies which exploited vascular endothelial growth factor (VEGF) neutralizing antibodies,  
5 such as bevacizumab [29], and those involving antiangiogenic tyrosine kinase inhibitors  
6 (TKIs), such as sunitinib or nintedanib, which target multiple receptors involved in  
7 angiogenesis [30-32]. As mentioned above, hypoxic tumor areas are characterized by  
8 increased expression of HIF1 $\alpha$  and its target MCT4, a lactate transporter which is often  
9 over-expressed by cells surrounding necrotic areas in solid cancers. In contrast, tumor  
10 areas relatively distant from the hypoxic zone preferentially express MCT1 - which  
11 predominantly acts as monocarboxylate importer [33] - and behave as OXPHOS-  
12 dependent regions. This pattern of tissue expression of MCT isoforms reflects a metabolic  
13 mosaicism, also termed metabolic symbiosis [30-32], which could derive from the effects  
14 of the tumor microenvironment, in particular the availability of oxygen and nutrients, on the  
15 metabolic plasticity of tumor cells (Figure 1).

16 Notably, however, in some experimental tumors treated with antiangiogenic drugs, such as  
17 bevacizumab, there is evidence of the existence of MCT4<sup>+</sup> tumor regions uncoupled from  
18 necrotic and *bona fide* hypoxic areas [36]. This observation, along with the metabolic  
19 characterization of *ex vivo* tumor cells obtained from tumors treated with anti-VEGF  
20 therapy [29], raises the hypothesis that in parallel with hypoxia-driven metabolic plasticity,  
21 antiangiogenic therapy could elicit *in vivo* selection of tumor cells with stable metabolic  
22 changes compared with the pre-treatment tumor, such as enhanced glycolysis [34]. This  
23 hypothesis underscores the possible existence of intra-tumor metabolic heterogeneity not  
24 only imposed by local pathophysiological conditions, such as hypoxia or glucose  
25 deprivation, or adaptation to a specific environment [35], but rather intrinsic to tumor cells.  
26 This type of metabolic heterogeneity is still poorly characterized and it could be connected

1 with the genetic heterogeneity of solid tumors, given the established link between certain  
2 oncogenes/tumor suppressors and metabolism (such as Akt/KRAS/glycolysis and  
3 MYC/glutaminolysis), or, alternatively, be accounted for by epigenetic mechanisms [36].  
4 One shared conclusion of the above quoted studies is the association between these  
5 metabolic changes and resistance to angiogenesis inhibition [37]. This novel mechanism  
6 of resistance is substantially new and it is not due to the bypassing of the vasculature  
7 blockade, given the fact that in the various models tumor growth occurred despite  
8 persistently reduced vascularization.

9 Intriguingly, genetic targeting of either the glycolytic part of the tumor (i.e. by genetic  
10 inactivation of MCT4) or the OXPHOS tumor region (by mTOR activity blockade) improved  
11 therapeutic activity of angiogenesis inhibitors. These results corroborate previous studies,  
12 which showed the possibility of improving therapeutic activity of sorafenib by modulating  
13 glycolysis with dichloroacetate (DCA) in hepatocellular carcinoma models [38] or by  
14 administration of bevacizumab plus drugs targeting carbonic anhydrase IX, an enzyme  
15 involved in pH regulation, in colon and glioblastoma models [39]. Along this line, some  
16 immunomodulatory drugs such as thalidomide and its derivatives have been recently  
17 shown to destabilize the cereblon-CD47-MCT1 axis [40], raising the possibility of exploiting  
18 thalidomide or related drugs to counteract increased MCT1/MCT4 expression associated  
19 with antiangiogenic therapy. Additional therapeutic approaches could focus on glycolysis-  
20 targeting drugs, such as LDHA inhibitors [41], which could possibly disclose enhanced  
21 therapeutic activity in tumors pre-treated with angiogenesis inhibitors, compared to  
22 untreated tumors, although some safety concerns exist related to these drugs and the field  
23 suffers from an historical lack of interest by the pharmaceutical industry [42].

24 Finally, since acquisition of this detrimental glycolytic phenotype seems to require chronic  
25 administration of the antiangiogenic drug, one may ask whether it might be possible to  
26 delay it by changing the schedule of administration of these drugs. Although interruption of

1 antiangiogenic therapy has been shown to negatively impact on angiogenesis control [43],  
2 from the viewpoint of metabolism it will be important to investigate how an intermittent  
3 schedule of treatment impacts on hypoxia, HIF1- $\alpha$  accumulation and metabolic mosaicism.  
4 One limitation of the published studies is that they were generally not designed to detect  
5 additional metabolic perturbations caused by antiangiogenic therapy, not involving  
6 glycolysis. In one study, however, Hanahan *et al.* investigated the metabolic profile of  
7 sunitinib-treated versus control tumors by a metabolomic approach, but they failed to  
8 disclose clear differences, assigning this negative finding to the intra-tumor metabolic  
9 heterogeneity [30]. Others, such as Keunen *et al.*, investigated by magnetic resonance  
10 spectroscopy the metabolic profile of glioblastoma xenografts treated with bevacizumab  
11 and found an increase in lactate and alanine metabolites, together with HIF-1 $\alpha$  induction  
12 and PI3K/AKT pathway activation [44]. Finally, Sounni *et al.* investigated the metabolic  
13 perturbations associated with sorafenib in breast cancer models and disclosed increased  
14 lipid metabolism during the re-oxygenation phase [45], whereas Bensaad *et al.* described  
15 up-regulation of fatty acid uptake and metabolism in tumors treated with bevacizumab,  
16 involving increased expression of FATBP3 and FATBP7 and accumulation of lipid droplets  
17 in tumor cells [46]. Given the existence of metabolic heterogeneity, which could represent  
18 a confounding factor, future studies in this area would greatly profit of new imaging  
19 methods, such as certain NMR techniques, which enable topographic imaging of  
20 metabolism in tumors [47]. In any case, whether these additional metabolic alterations  
21 contribute to acquired resistance to antiangiogenic drugs is currently unknown.

22

### 23 **Targeted therapy and metabolism changes**

24 Apart from antiangiogenic therapy, also resistance to other targeted therapies seems to  
25 involve metabolic adaptation of tumors cells. For instance, resistance of breast cancer  
26 cells to the HER-2-targeting trastuzumab has been associated with increased glycolysis

1 via heat shock factor 1 and LDHA up-regulation and combining trastuzumab with  
2 glycolysis inhibitors synergistically inhibited trastuzumab-sensitive and -resistant breast  
3 cancers both *in vitro* and *in vivo* [48].

4 Along this line, pancreatic adenocarcinoma cell lines resistant to the multi-tyrosine kinase  
5 inhibitor axitinib show increased activated Akt and up-regulation of glucose uptake *in vitro*,  
6 due to the membrane re-localization of the glucose transporter GLUT1, as well as  
7 increased glycolytic activity [49]. Indeed, interference with a phosphatidylinositol-3 kinase  
8 (PI3K) inhibitor reversed the GLUT1 translocation and restored sensitivity to axitinib  
9 treatment.

10 Finally, a recent study on NOTCH1-addicted T acute lymphoblastic leukemia (T-ALL)  
11 disclosed that resistance to  $\gamma$ -secretase inhibitors (GSI) - a class of drugs able to block  
12 NOTCH1 signaling - was associated with prominent metabolic reprogramming involving  
13 both glycolysis and glutaminolysis in a mouse model of Pten-deficient T-ALL [50].  
14 Moreover, genetic and pharmacologic inhibition of glutaminase was highly synergistic with  
15 inhibition of NOTCH1 signaling in T-ALL cell lines and patient-derived T-ALL xenografts.  
16 More broadly, these results underscore the importance of metabolic rewiring in the context  
17 of resistance to targeted therapies and demonstrate that secondary mutations, such as  
18 those in PTEN in the case of T-ALL, can greatly impact of the metabolic profile of tumors.  
19 It can be speculated that ongoing studies will soon uncover similar mechanisms in other  
20 types of tumors resistant to targeted therapy.

21

## 22 **Conclusions**

23 Although it is widely accepted that metabolic rearrangements are essential to satisfy the  
24 different requirements of a cancer cell during tumorigenesis, the metabolic reprogramming  
25 in response and adaptation to anti-tumor therapies has been perceived as a bystander  
26 effects of molecular and genetic rearrangements. The current manuscript gathers recent

1 findings in metabolic reprogramming and anti-tumor therapy response and suggests that  
2 such reprogramming is essential for the acquisition of a resistant phenotype. Importantly,  
3 different drugs can select different metabolic phenotypes in the resistant cancer cells  
4 ultimately impacting on tumor plasticity: such plasticity seems to be crucial to resist the  
5 stress induced by therapies. In summary, it is plausible to affirm that the ability to rewire  
6 proliferative and pro-survival networks that characterizes aggressive/resistant cancer cells  
7 is functional to confer them a high degree of metabolic plasticity to respond and react to  
8 external stress stimuli, such as those triggered by anti-tumor agents.

9

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13

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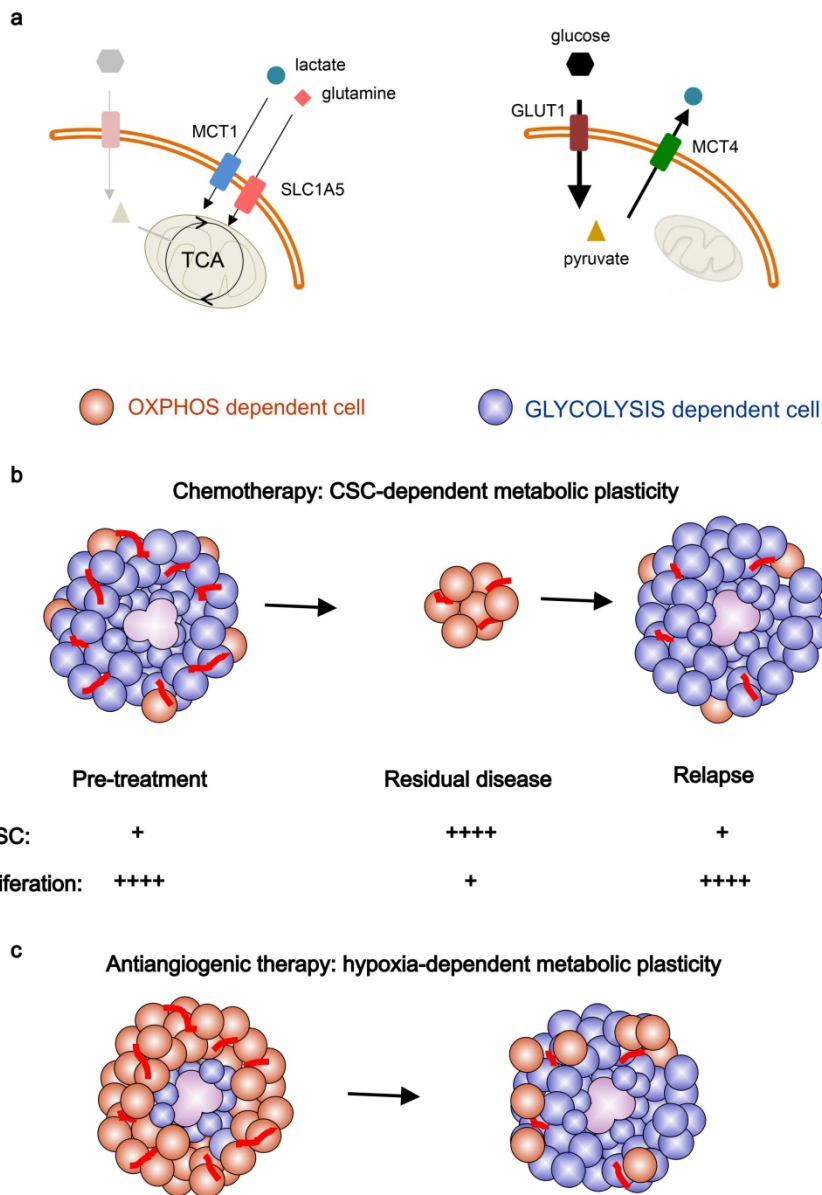
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**Figure 1**

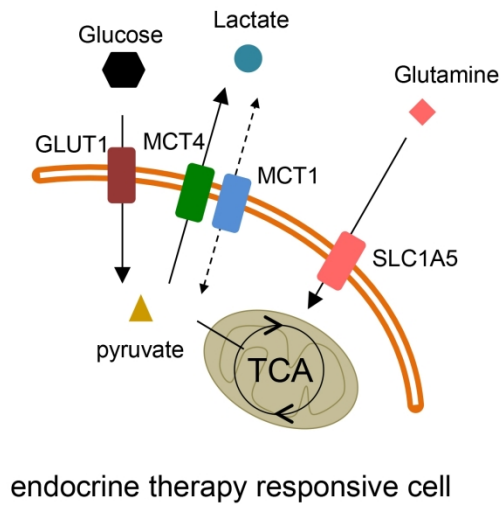


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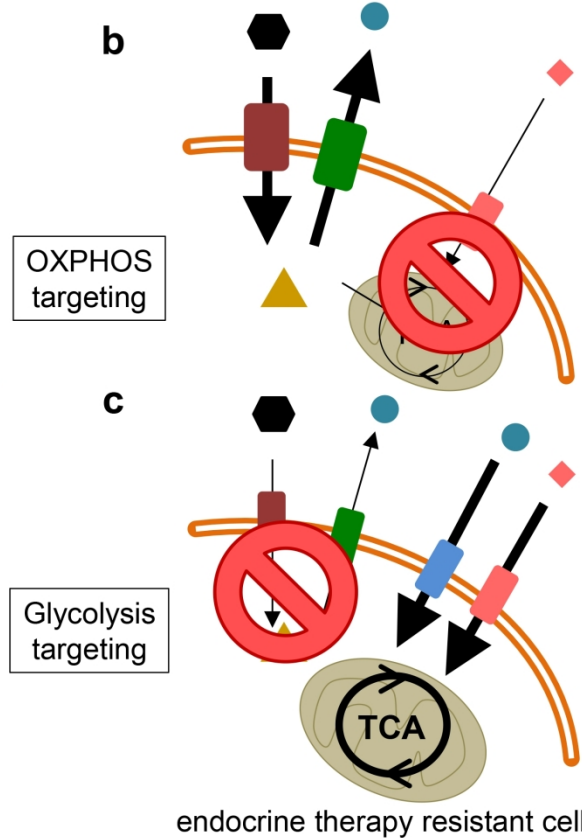
2 **Figure 1.** Metabolic plasticity in the context of cancer therapy. Before treatment, it is  
 3 envisioned that both OXPHOS- and glycolysis-dependent cells co-exist in the tumor (a).  
 4 Chemotherapy may impact on cancer stem cell (CSC)-dependent metabolic plasticity.  
 5 According to this model, the final metabolic phenotype of the tumor depends on its content  
 6 of CSC versus non-CSC populations (b). In contrast, antiangiogenic therapy could  
 7 primarily trigger hypoxia-dependent metabolic plasticity, involving topographic distribution  
 8 of cancer cells endowed with different metabolic phenotype in tumor areas exposed to  
 9 various concentrations of oxygen and nutrients (c).

Figure 2

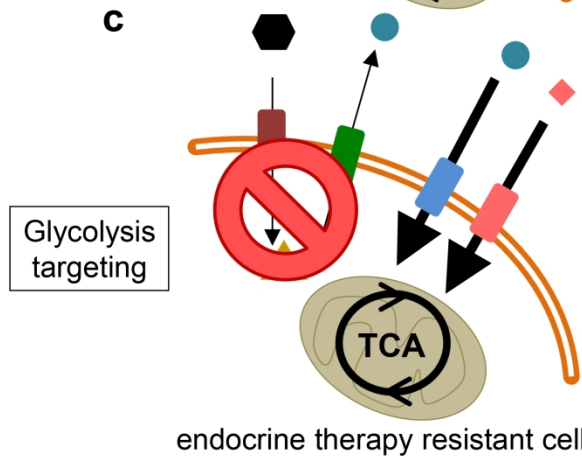
a



b



c



1

2 **Figure 2.** ER positive endocrine therapy (ET) responsive breast cancer cells are  
3 characterized by a basal metabolism that predominantly undergoes OXPHOS with a  
4 partial release of lactate (a). Indeed, these cells are sensitive to both glycolysis and  
5 OXPHOS blockade. When becoming ET-resistant, cancer cells display higher uptake of  
6 glucose and are insensitive to OXPHOS targeting (b). However, targeting glycolysis is  
7 substantially ineffective, due to the ability of cancer cells to rewire their metabolic  
8 pathways, thus acquiring OXPHOS dependency (c).

9