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Lactic acid fermentation: A maladaptive mechanism and an evolutionary throwback boosting cancer drug resistance

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ABSTRACT

After four decades of research primarily focused on tumour genetics, the importance of metabolism in tumour biology is receiving renewed attention. Cancer cells undergo energy, biosynthetic and metabolic rewiring, which involves several pathways with a prevalent change from oxidative phosphorylation (OXPHOS) to lactic acid fermentation, known as the Warburg effect. During carcinogenesis, microenvironmental changes can trigger the transition from OXPHOS to lactic acid fermentation, an ancient form of energy supply, mimicking the behaviour of certain anaerobic unicellular organisms according to "atavistic" models of cancer. However, the role of this transition as a mechanism of cancer drug resistance is unclear. Here, we hypothesise that the metabolic rewiring of cancer cells to fermentation can be triggered, enhanced, and sustained by exposure to chronic or high-dose chemotherapy, thereby conferring resistance to drug therapy. We try to expand on the idea that metabolic reprogramming from OXPHOS to lactate fermentation in drug-resistant tumour cells occurs as a general phenotypic mechanism in any type of cancer, regardless of tumour cell heterogeneity, biodiversity, and genetic characteristics. This metabolic response may therefore represent a common feature in cancer biology that could be exploited for therapeutic purposes to overcome chemotherapy resistance, which is currently a major challenge in cancer treatment.

1. The metabolism “revival” in tumour biology

Cellular metabolism and metabolic plasticity in tumour cell biology are gaining renewed interest in the scientific community [1]. After the pioneering works of Otto Warburg [2,3] and Albert Szent-Gyorgyi [4–6] in the 1930s, and the long “golden age” period of genetic studies in cancer, dysregulation of cellular metabolism has again been reconsidered as an important hallmark of cancer [1]. Specific metabolic pathways have been implicated in promoting tumorigenesis [7,8], and glycolysis, lactic acid fermentation, and oxidative phosphorylation (OXPHOS) are processes that are actively studied as targets for inhibiting tumour growth and overcoming drug resistance. In general, the metabolic axis *glucose→pyruvate→TCA/OXPHOS (oxidative glycolysis)* is normally working in non-tumour cells, whereas tumour cells shift towards a lactate fermentation metabolic profile, *glucose→pyruvate→lactate (fermentative glycolysis)*. The fermentation profile of cancer cells is defined as the Warburg effect, aerobic glycolysis in which pyruvate is converted to lactic acid (lactic acid fermentation), regardless of normoxic or anoxic conditions [9]. Although this “archaic” process, typical of prokaryotes or unicellular eukaryotic organisms, is not energetically efficient (36 vs 4 ATP molecules generated/mol of glucose), tumour cells mostly rely on it for energy production [10]. The “switch” toward a fermentative glycolysis phenotype provides multiple benefits to tumour cells, including rapid ATP biosynthesis, a more efficient supply of biosynthetic intermediates [10], and reduced production of reactive oxygen species (ROS), thereby protecting cancer cells from apoptosis [11]. Two steps are central and highly regulated: the conversion of pyruvate into lactate, which is catalysed by lactate dehydrogenase (LDH), and the activation of OXPHOS. Here, it is important to underline that a tumour can be depicted as an "integrated metabolic ecosystem", in which some cells mostly rely on glycolysis whereas others show lactate fuelled OXPHOS. In some way, a tumour can be considered a "colony", where some cells shift to lactic acid production to provide energy to other cells, which oxidise it [12]. So, the Warburg effect can be

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considered as a “global metabolic remodelling”, a way by which tumour cells reorganise and rearrange their metabolism to manage energy production and biosynthetic activity in the absence of OXPHOS. Thus, the Warburg effect implies not only fermentative glycolysis, but also glutaminolysis, which provides additional ATP molecules, and more lactate, and is important for the biosynthesis of nucleic acids, fatty acids, and cholesterol [12]. In addition, to provide the necessary reducing capacity and biosynthetic intermediates, tumour cells also divert part of the glucose to the pentose phosphate pathway (PPP) [13,14], thereby producing more reduced glutathione (GSH), which in turn reduces drug sensitivity [15,16]. A correlation between reduced ROS production and increased drug resistance has now been reported [17,18].

How the Warburg effect is triggered is still debated. Hypoxia is thought to be an activating stimulus and has recently been ruled out as a major factor, as some tumours develop the Warburg effect even under normoxic conditions [10]. Some authors have proposed that increased demand for NAD + - mismatched with an adequate supply of ATP - can activate the Warburg phenotype [19]. The earliest steps in the activation of the Warburg effect should be sought in the altered metabolic control required for tumour cells to acquire cell-autonomous nutrient uptake and anabolic characteristics. However, the nature of this alteration has not been fully elucidated, and the mechanisms by which the Warburg phenotype supports drug resistance are still debated. Indeed, it is known that the glycolytic environment can affect the response of cancer cells to drugs, but the exact reasons and mechanisms have not been fully elucidated [20]. As the relevance of the Warburg effect in tumorigenesis and drug resistance is still under debate [11,20], the role of OXPHOS in cancer biology is also debated. For example, certain studies have shown that defective OXPHOS promotes tumorigenicity in HCC [21,22], while others have reported inhibition of OXPHOS as a therapeutic strategy for HCC [23,24]. Similar divergences have also been reported in other types of malignancies [25,26]. Furthermore, the regulatory role of OXPHOS on key metabolites such as lactate has not been fully elucidated [27]. In this regard, metabolic reprogramming-driven drug resistance appears to be present in different types of cancer, even if the nature of the reprogramming is different. For example, in ovarian cancer cells, drug resistance was associated with an increase in fatty acid uptake and decreased glucose uptake and lipogenesis, suggesting a shift from glucose to fatty acid energy metabolism [28]. However, not all metabolic rearrangements lead to drug resistance. For example, increased aerobic glycolysis and de novo lipogenesis (DNL), as well as decreased urea cycle, were detected in hepatocellular carcinoma (HCC), but no association with drug resistance was observed [29].

Here, we propose that modulating the balance between OXPHOS and lactic acid fermentation toward the activation of OXPHOS and inhibiting fermentation can be a strategy to ameliorate tumour aggressiveness and drug resistance. To this end, we recently demonstrated that inhibition of OXPHOS in favour of lactic acid fermentation enhances drug resistance in HCC [30]. Based on this observation, we believe that approaches to modulate the metabolism of fermentative tumour cells will provide tools to overcome drug resistance in cancer. In particular, we propose the activation of OXPHOS and the inhibition of lactic acid fermentation to reduce tumour growth and drug resistance. If so, then induction of this metabolic phenotype is expected to be independent of the genetic background of each tumour, and this could be exploited for therapeutic purposes.

2. “Atavistic reversion” as a new paradigm to understand tumour biology

After the first observations made by Warburg [2,3], Szent-Gyorgy [4–6] and Weinhouse [31], evidence has been collected in recent years supporting the idea that tumour cells switch to lactic acid fermentation, shutting down OXPHOS regardless of the oxygen availability (i.e., the Warburg effect). Metabolic transitions from OXPHOS to fermentation also occur in other organisms, including prokaryotes (bacteria) and unicellular eukaryotes (yeast) under certain environmental conditions [32]. Somehow, the evolutionary transition from bacteria to yeast to multicellular metazoans was characterised by a phenotypic shift from an undifferentiated/proliferative/fermentative state to a differentiated/quiescent/oxidative state (Fig. 1). A biochemical similarity between the yeast Saccharomyces cerevisiae and tumour cells has been highlighted, and some enzymes, such as phosphofructokinase (PFK), pyruvate kinase (PK), lactate dehydrogenase (LDH) and succinate dehydrogenase (SDH) have been suggested as possible effectors for the metabolic switch operating in yeasts [33]. In the same line of principle, under hypoxic conditions, mammalian skeletal muscle transiently switches from an oxidative to a lactic fermentative metabolism, and this reminds tumour cell behaviour and supports the conservation of “ancient” metabolic processes in multicellular eukaryotes [34]. Indeed, the resemblance between prokaryotes, unicellular metazoan (yeasts) and tumour cells has been pointed out from a tumour biology perspective (Fig. 2). In fact, the idea of cancer as a “devolution” process” towards an ancient nucleated, pre-multicellular level was suggested almost forty years ago. Setala proposed mutagen-induced mitochondrial damage as a driver of transformation and “devolution”, due to a “deficit in energy generation” [35]. More recently, some papers have extended this line of evidence and proposed that cancer is an “atavistic” re-emergence and activation of genes of prokaryotic/unicellular eukaryotes' origin [36], which are kept “dormant” in normal multicellular eukaryotic cells [37]. The activation of “atavistic” programs can be determined by dysregulations in the interactions between prokaryotic and eukaryotic genes, conferring adaptability and aggressiveness to cancer cells [38]. This altered interaction may be due to somatic mutation of regulatory genes at the interface between genes of unicellular and multicellular processes [39]. Interestingly, according to the “atavistic reversion” theory, the “resurfaced” ancient metabolic processes show more biological robustness compared with their normal eukaryotic counterpart [39]. This is a key point, as current therapies target the robustness and strength of cancer cells, not their weaknesses. For example, it is desirable to inhibit fermentation and promote OXPHOS and differentiation rather than target cell proliferation. Indeed, both fermentation and proliferation are strengthened “cores” deeply preserved by evolution. Based on these observations, a new Systemic Evolutionary Theory of Cancer (SETOC) was recently proposed, which suggests that a general change in the environmental conditions can trigger the "awakening” of cellular modules typical of prokaryotes or unicellular eukaryotes [40–43]. Eliciting stimuli, such as chronic inflammation, damage to mitochondrial membrane or modifications of its chemical composition by diverse chemical stressors may lead to an uncoupling of the balance between the two “coexisting systems” in favour of the “ancestral” programs, eventually causing cancer development. According to this theory, new approaches to cancer therapy should be considered and adopted in line with the paradigm shift “from single molecular targets to process-focused systems strategies”. This is what we define as a “process-based system pharmacology” [40].

3. Lactic acid fermentation as a "driver" of malignancy and drug resistance

As we highlighted above, alterations in cellular metabolism are strongly associated with tumorigenesis and drug resistance

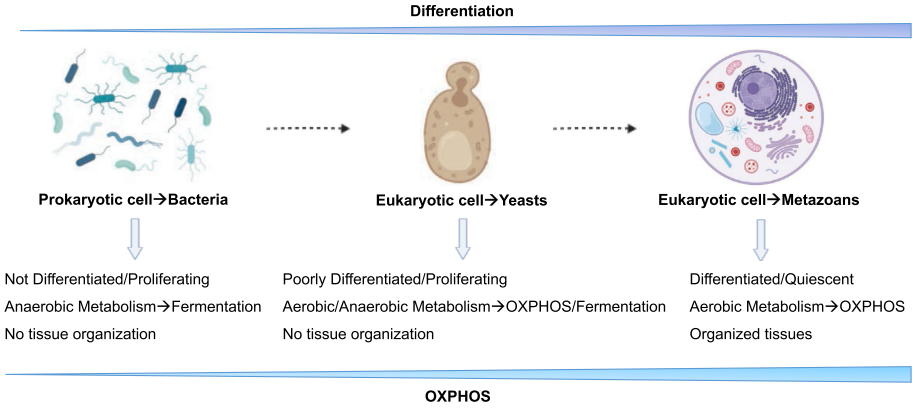

Fig. 1. An increase in biological complexity is associated with a transition from an anaerobic/fermentative metabolism to oxidative phosphorylation-dependent metabolism. The current knowledge about the acquisition of morphological and biochemical complexity, from prokaryotes to unicellular eukaryotes, to metazoan pluricellular eukaryotes is summarised. Illustrations were created using biorender.com.

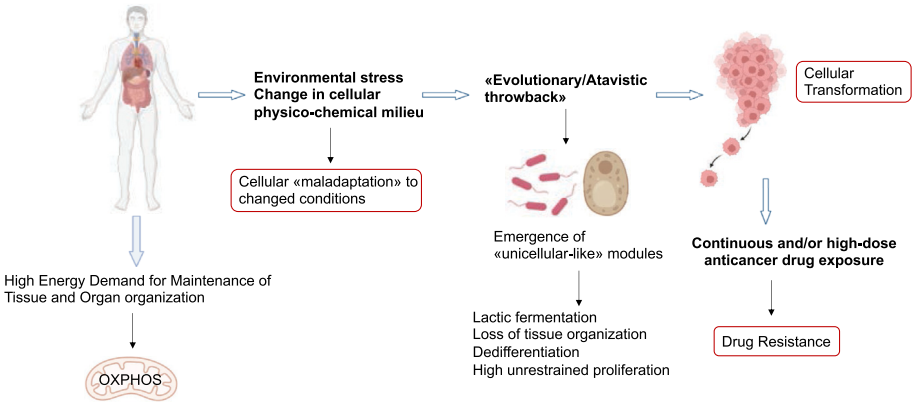

Fig. 2. "Evolutionary/Atavistic reversion" theory explaining tumorigenesis and drug resistance. This theory can provide an interpretative model for cellular transformation and the acquisition of drug resistance. Illustrations were created using biorender.com.

[44–47]. Interestingly, recent observations in naked-mole rats support the role of lactate fermentation and the Warburg effect in tumorigenesis. These rodents live underground where they are well-adapted to hypoxic conditions with no need to switch their metabolism to lactic acid fermentation and the Warburg effect. Notably, despite their long lifespan, these rats have an extremely low incidence of cancer compared to other rodents [48]. This is in line with the evidence that lactic acid fermentation sustains the malignant phenotype.

3.1. Lactic acid fermentation and drug resistance

Drug resistance is now one of the trickiest issues in clinical oncology and a "hot topic" in tumour biology research [49]. As we mentioned above, the role of fermentative metabolism and OXPHOS in tumorigenesis and drug resistance is still under debate. We can consider sorafenib resistance, one of the most widely employed chemotherapeutic agents for HCC, as a paradigm of the role of fermentation in drug resistance. Indeed, sorafenib resistance is a concerning problem in the management of therapeutic interventions for advanced HCC. Several mechanisms have been reported on how cells become resistant to sorafenib. Mostly, they focus on the dysregulation of signalling pathways [47] or the differentiation state [46]. For instance, the effectiveness of sorafenib was higher in well-differentiated and wild-type p53-expressing cells, such as HepG2, which display a higher oxygen consumption rate (OCR), compared with poorly differentiated HCC cells [46]. Still, these mechanisms cannot fully explain how the cells acquire resistance. To date, there is no clear evidence linking tumour cell metabolism to sorafenib sensitivity. For example, inhibition of OXPHOS has been proposed as a therapeutic strategy in HCC [23,24]. Similarly, in drug-resistant AML [50] and NSCLC cell lines [24], OXPHOS inhibition increased sensitivity to drug therapy, which was also observed in other cancer cell lines [51]. Conversely, others reported that defective OXPHOS prompted tumorigenicity in HCC [21,22], induced a glycolytic phenotype leading to chemoresistance [52] and stimulated OXPHOS boosting the sensitivity of HCC to biguanide drugs [53]. Furthermore, activation of OXPHOS by the pyruvate dehydrogenase kinase inhibitor dichloroacetic acid (DCA) can overcome sorafenib resistance in HCC [54]. Consistently, aerobic glycolysis has been suggested as a drug resistance mechanism in HCC [55,56]. What we describe above has been also reported in other types of cancer and is in line with "cancer heterogenicity/mosaicism", where some cells rely on the Warburg effect/lactic fermentation, whereas other cells still use OXPHOS [57]. In this context, our hypothesis suggests that continuous or high-dose anticancer drug exposure induces a wide metabolic switch/rearrangement in tumour cells that promotes the fermentative phenotype at the expense of OXPHOS. Thus, in cancer heterogenicity, drug-resistant cancer cells will prevail and rely heavily on the fermentative phenotype (Fig. 4). In our idea, fermentation is regarded as an "atavistic" trait due to the common "ancestral"

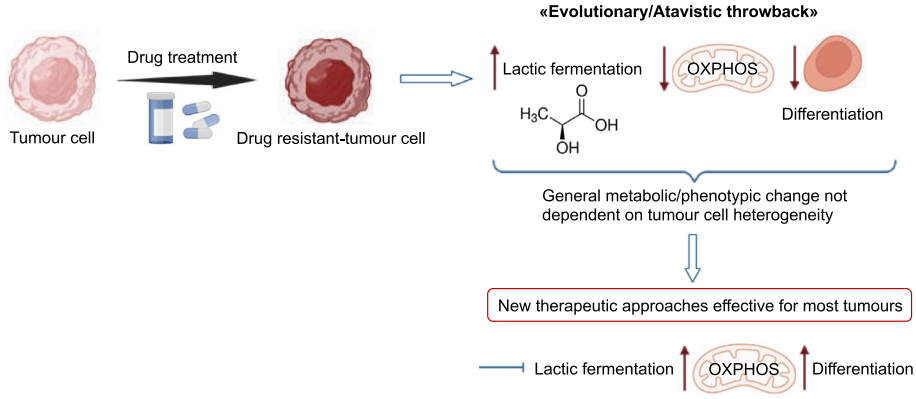

Fig. 3. "Evolutionary throwback-drug resistance" hypothesis. This hypothesis proposes that lactic acid fermentation is a "maladaptive evolutionary throwback" boosting and sustaining drug resistance in tumour cells. Illustrations were created using biorender.com.

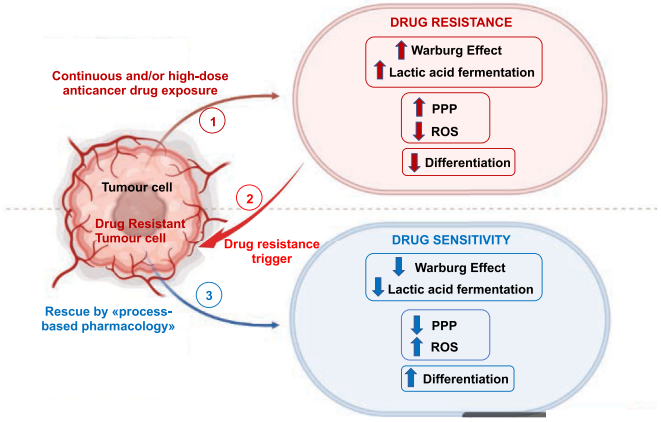

Fig. 4. Schematic representation of drug-induced metabolic rearrangement leading to chemotherapy resistance in tumour cells and rescuing interventions according to - the proposed "evolutionary throwback-drug resistance" hypothesis. Illustrations were created using biorender.com.

origin of all metazoan cells, "awakened" as an adaptive response of cells to a chronic challenge (e.g., microenvironment changes, chemotherapy drugs, toxins, etc.): hence, metabolic plasticity is the way how cells respond and adapt to it. Similarly, metabolic rearrangements can also be involved in the response to challenges such as chronic or high-dose chemotherapy, leading to drug resistance. For this reason, pharmacological interventions aimed at rescuing respiration and differentiation may lead to the restoration of drug sensitivity.

3.2. Lactic acid fermentation and the Warburg effect in differentiation, development and and tumour cell biology

Several pieces of evidence are available on the correlation between lactic fermentation, cellular dedifferentiation, and tumorigenesis. For example, during hepatic differentiation, OXPHOS activity is increased, due to the stimulation of mitochondrial biogenesis and mitochondrial protein expression. An opposite pattern was observed during the spontaneous dedifferentiation of primary hepatocytes [58] as well as the transition from hepatic specification to hepatic maturation was shown to be dependent upon mitochondrial respiration [59]. Interestingly, the level of oxygen regulates the differentiation of hepatocytes: hypoxia maintains stem cell features and inhibits differentiation, whereas hyperoxia stimulates differentiation [60]. The correlation between metabolism and differentiation has also been described in other processes, including osteogenesis [61] and myocardial differentiation [62]. Some reports have also linked differentiation and metabolic status to tumorigenesis. For example, human tumour hepatocyte dedifferentiation/retro-differentiation to embryonic stem cells is associated with decreased mitochondrial activity and high lactate production leading to chemo-resistance [63]. It is worth highlighting here the metabolic analogy between tumorigenesis and embryogenesis [64,65]. Indeed, during development, the Warburg phenotype has been observed across evolutionary lineages, from *Drosophila* to sea urchins to zebrafish to mammals [66]. When required, this switch confers a selective growth advantage that is repressed upon differentiation. In general, a metabolic rearrangement from glycolysis to OXPHOS is observed during stem cell differentiation, where dependence on glutamine is also observed [67]. Finally, it is important to mention here that well-differentiated tumour cells display a higher degree of OXPHOS compared with undifferentiated anaplastic cancer cells. For example, this feature is well exemplified in HCC cell lines [68]. Taken together, these observations support the idea of an inverse relationship between glycolytic metabolism and differentiation, where undifferentiated/dedifferentiated tumour cells are metabolically supported by lactic acid fermentation/Warburg effect, along with the contribution of the PPP, to sustain biosynthetic activity and redox control.

4. Lactic acid fermentation as a "maladaptive evolutionary throwback" driving transformation and drug resistance in cancer

In general, a global "metabolic rearrangement" is operating in cancer cells and several pathways may be involved [10,69]. Our hypothesis is based on the idea that lactic acid fermentation and the Warburg effect can be considered as a common trait in this rearrangement, a sort of "maladaptive evolutionary throwback", leading to a "recall" of metabolic programs typical of more primitive forms of life, such as prokaryotes and unicellular eukaryotes, which is "embedded" in all eukaryotic metazoan cells. In support of this idea, in addition to the Warburg effect, the PPP has also been found in several bacteria [70] and yeasts [71], similar to that observed in cancer cells. This metabolic shift would occur as a "maladaptive" response of normal cells to chronic challenges (e.g., microenvironment changes, drugs, toxins, etc). Similarly, when tumours are challenged with high-intensity stimulations, such as continuous and/or high-dose exposure to a chemotherapeutic drug,

cancer cells would respond with an “intensification” of their lactic acid production and Warburg phenotype. In our view, this metabolic adaptation is “awakened” in these peculiar challenging conditions (Fig. 3). It is worth mentioning here the role of the PPP in increasing intracellular ROS in both cancer cells and bacteria, and the link of this metabolic pathway to decreased drug responsiveness [15]. In line with the promotion of the Warburg phenotype by drugs, we recently demonstrated that ectopic expression of lysophosphatidic acid receptor 6 (LPAR6) in HCC cells determines sorafenib resistance by triggering a “metabolic switch” that boosts lactic acid fermentation at the expense of OXPHOS. This sorafenib resistance can be overcome by reducing lactic acid fermentation by inhibiting LPAR6 using novel LPAR6 antagonists [30] that we recently developed [72,73]. LPAR6 has a pro-tumorigenic role in HCC, and its overexpression leads to poorer clinical outcomes in HCC patients [74]. Here, we propose that such a "glycolytic remodelling", due to drug treatment and driven by a higher glucose dependence of cancer cells, can be regarded as a general phenotypic mechanism operating in all tumour cells, regardless of the tumour cell heterogeneity, biodiversity and genetic background. The basis of this shared behaviour lies in the strength of the evolution of ancestral programs conserved in eukaryotic cells [40–43,75,76]. If confirmed, our hypothesis would provide new efficacious theoretical and translational tools to cope with drug resistance in cancer. Based on this view, it is possible to conceive therapeutic “toolkits” using blends of compounds that inhibit the fermentation process and activate OXPHOS along with the promotion of cellular differentiation. In this regard, it is worth emphasising that lactic acid fermentation is a metabolic signature of unicellular organisms, in contrast to multicellular organisms that rely primarily on OXPHOS (Fig. 1). This observation strengthens the notion that cancer can be interpreted as the “emergence” of unicellular organism traits, evolutionary “embedded” in eukaryotic cells [40–43,75,76] (Fig. 2). Reactivation of OXPHOS at the expense of glycolysis and promotion of differentiation inhibits the “ancestral” unicellular fermentative phenotype, eventually increasing drug responsiveness (Fig. 3). To this end, we will test novel compounds capable of activating OXPHOS and stimulating differentiation, which will be associated with selective chemical inhibitors of lactate dehydrogenase (LDH). More broadly, our hypothesis will lead us to delve deeper into the balance between OXPHOS and lactic acid fermentation to determine cancer cell behaviour and the development of resistance to drug-based therapies. Our hypothesis, which encompasses a “metabolic atavistic throwback", will provide a valuable interpretative model to study the biological bases of carcinogenesis and drug resistance, as well as the theoretical background to develop new therapeutic options in oncology.

5. Conclusive remarks

The balance between lactic acid fermentation and OXPHOS is a central point in tumour cell metabolism even though the mechanisms by which this is regulated are still not fully understood. Here, we propose that lactic acid fermentation supports drug resistance and this may provide important explanatory theoretical models and tools for basic and translational oncology. In line with the “atavistic reversion theory” of cancer, we postulate a central role of lactic acid fermentation in drug resistance. Our recent study showed that an LPAR6-triggered metabolic switch from OXPHOS to lactic acid fermentation resulted in resistance to sorafenib in HCC [30]. Therefore, we hypothesised that lactic acid fermentation-driven drug resistance could be considered a more general phenotypic response of tumour cells, regardless of the specificity and heterogeneity of different cell types. Our hypothesis can provide the theoretical basis for the development of new therapeutic opportunities based on the inhibition of lactic acid fermentation, activation of OXPHOS and promotion of differentiation. On the one hand, from the perspective of basic science, our next step is to study the mechanisms linking metabolism, differentiation, and drug resistance. On the other hand, from a translational perspective, our approach could help overcome drug resistance, which is one of the highest clinical concerns in cancer management today.

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