15 Exploiting Cancer Cells Metabolic Adaptability to Enhance Therapy Response in Cancer

Sofia C. Nunes

Abstract

Despite all the progresses developed in prevention and new treatment approaches, cancer is the second leading cause of death worldwide, being chemoresistance a pivotal barrier in cancer management. Cancer cells present several mechanisms of drug resistance/tolerance and recently, growing evidence have been supporting a role of metabolism reprograming per se as a driver of chemoresistance. In fact, cancer cells display several adaptive mechanisms that allow the emergency of chemoresistance, revealing cancer as a disease that adapts and evolve along with the treatment. Therefore, clinical protocols that take into account the adaptive potential of cancer cells should be more effective than the current traditional standard protocols on the fighting against cancer.

In here, some of the recent findings on the role of metabolism reprograming in cancer chemoresistance emergence will be discussed, as the potential evolutionary strategies that could unable these adaptations, hence allowing to prevent the emergency of treatment resistance, changing cancer outcome.

Keywords

Adaptation · Cancer · Chemoresistance · Evolution · Metabolism

15.1 Cancer: From Hanahan and Weinberg to Darwin

Despite all the progresses developed in prevention and new treatment approaches, cancer is the second leading cause of death worldwide (Fitzmaurice et al. 2015). In accordance with the International Agency for Research on Cancer, 14.1 million cancer cases (Ferlay et al. 2013a) and 8.2 million cancer deaths (Ferlay et al. 2013b) were estimated worldwide in 2012. For 2020, 17.1 million incidences and 10.05 million cancer deaths (Ferlay et al. 2013a) are estimated. Metastatic disease accounts for over 90% of all cancer-related deaths, where the treatment with surgery, conventional chemotherapy and radiation is ineffective (Rankin and Giaccia 2016). The late diagnosis combined with resistance to the conventional anti-cancer drugs used, are the major causes of cancer poor prognosis.

More than 200 different types of cancer exist (cancerresearchuk.org 2018), however, the physiological alterations that entail the malignant transformation were proposed to be common to the majority or even to all types of human tumours (Hanahan and Weinberg 2000). Therefore, in

S. C. Nunes (✉)
CEDOC, Chronic Diseases Research Centre, NOVA Medical School | Faculdade de Ciências Médicas, Universidade NOVA de Lisboa, Lisbon, Portugal

Instituto Português de Oncologia de Lisboa Francisco Gentil (IPOLFG), Lisbon, Portugal

J. Serpa (ed.), *Tumor Microenvironment*, Advances in Experimental Medicine and Biology 1219,
https://doi.org/10.1007/978-3-030-34025-4_15

2000, Hanahan and Weinberg proposed the existence of six core hallmarks of cancer cells: self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion of programmed cell death, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis (Hanahan and Weinberg 2000). Eleven years later, the authors revisited those original hallmarks, and included energy metabolism reprogramming and evading immune destruction, as emerging hallmarks of cancer (Hanahan and Weinberg 2011). Underlying these hallmarks, the authors suggested two consequential characteristics of neoplastic cells that facilitate the acquisition of both core and emerging hallmarks: genome instability, and inflammation (Hanahan and Weinberg 2011). The acquisition of these hallmarks is an evolutionary process, involving natural selection among the neoplastic cells, allowing cancer initiation, progression and chemoresistance (Crespi and Summers 2005). In fact, cancer cells evolve under the same rules as Darwin's finches on the Galapagos, in which several genetically heterogeneous individual cells share the tumour microenvironment, competing for growth and survival in continuously changing environments (Polyak 2007).

Cairns and Nowell firstly introduced the evolutionary perspective to cancer. In 1975, Cairns had argued cancer as an evolutionary process, driven by mutation and natural selection (Cairns 1975). In 1976, Nowell's proposed that the majority of neoplasms present a unicellular origin, and that the tumour progression results from acquired genetic variability within the original clone, allowing the sequential selection of more aggressive subclones (Nowell 1976). Nowell have then established the clonal evolution theory of tumour progression (Nowell 1976).

Besides being an evolutionary process, cancer is also an ecological process, being cancer cells subject to competition for space and resources, predation by the immune system and cooperation to disperse and colonise new organs (Axelrod et al. 2006; Merlo et al. 2006). Strengthening the relevance of evolution and ecology on cancer, recently, Maley and colleagues have developed an evolutionary and ecological classification system for neoplasms in order to improve the clinical management of cancer. Hence, the authors proposed the classification of neoplasms based on the Evo-index, including the intratumoural heterogeneity and its changes over time, and the Eco-index, including the hazards to neoplastic cell survival and the resources available to these cells (Maley et al. 2017).

Hypoxia and acidosis are common features of the tumour microenvironment, being highly selective and inducing genetic instability, hence promoting somatic evolution (Gillies et al. 2012). Cytotoxic anti-cancer drugs also drive evolution of cancer cells, by imposing strong evolutionary selection pressures on the surviving cells (Gillies et al. 2012).

We have to highlight that besides genetic variation, other non-genetic features as epigenetic mechanisms may also be pivotal for the adaptation of cancer cells to new environments. In fact, Salgia and Kulkarni have recently published a reflexion on this duality of genetic/non-genetic features of chemoresistance (Salgia and Kulkarni 2018) that merits further attention.

In the next section, I will focus on some metabolic adaptive strategies that cancer cells undergo in order to cope with anti-cancer drugs, allowing disease progression and resistance to treatment.

15.2 Metabolism Reprograming in Cancer: A Driving Force of Adaptation to Challenging Environments

The metabolism reprograming is well known to be a key feature of tumorigenesis and recently, evidence have been supporting also a role of altered metabolism in anti-cancer drugs response and adaptation (Morandi and Indraccolo 2017).

The best characterised metabolic phenotype observed in tumour cells is the Warburg effect, proposing that cancer cells present increased rate of glycolysis even under normal oxygen concentrations due to defective mitochondrial oxidative phosphorylation (OXPHOS) (Warburg 1956). However, evidence accumulate showing that mitochondrial OXPHOS function is intact in

most tumours (Alam et al. 2016; Guppy et al. 2002; Rodríguez-Enríquez et al. 2000, 2006; Viale et al. 2015). Moreover, evidence also support that the bioenergetics of tumour cells is highly complex, where cancer cells have the ability to use several substrates in order to support energy production, including glucose, glutamine, fatty acids, and acetate (Alam et al. 2016). Also, within a tumour, subpopulations of cells with glycolytic and oxidative metabolisms coexist, enhancing metabolic plasticity and improving tumorigenesis and metastasis (Viale et al. 2015; Yu et al. 2017), hence highlighting the metabolic complexity of cancer cells that allows coping with changing environments. Recent studies have disclosed the Warburg effect as a way of cancer cells to sustain cell proliferation rather than producing energy (Liang et al. 2017; Liu and Yin 2017; Lopes-Coelho et al. 2017), once the glycolytic intermediates are deviated to serve as building blocks needed for replicating DNA and cellular machinery prior to mitosis (Lopes-Coelho et al. 2017). Other hypothesis that explain the advantage of the Warburg effect on cancer cells is that it supports an ideal tumour microenvironment, sustaining cancer cells proliferation (e.g. acid-mediated invasion hypothesis) and that altered glucose metabolism alters cancer cell signalling, promoting tumorigenesis via reactive oxygen species (ROS) and the modulation of chromatin state (reviewed in (Liberti and Locasale 2016)).

In the next section, the mechanisms of drug resistance will be briefly addressed and the role of metabolic reprograming *per se* as a driver of cancer cells adaptation and resistance to anti-cancer drugs will be discussed.

15.3 Metabolism Reprograming as a Driver of Cancer Cells Adaptation and Resistance to Anti-cancer Drugs

Drug resistance can be intrinsic (exists prior to treatment) or acquired during treatment (Holohan et al. 2013) and two general causes of drug resistance/tolerance exist: host factors and specific genetic or epigenetic alterations in the cancer cells (Gottesman 2002). Importantly, tumours present a high molecular heterogeneity (Swanton 2013), allowing therapy-induced selection of a resistant subpopulation of cells, thus leading to drug resistance emergence (Holohan et al. 2013).

As Salgia and Kulkarni emphasized, drug resistance, tolerance and persistence terms have been ambiguously and inadvertently used (Salgia and Kulkarni 2018). Whereas genetics strongly underlies drug resistance, tolerance may be inherited or not and is commonly used to describe the survival capacity upon the transient exposure to high drug concentrations. Persistence refers to the survival capacity of a subpopulation of a clonal population upon the exposure to high drug concentrations (Salgia and Kulkarni 2018).

Several mechanisms were already associated with drug resistance/tolerance, including the increased drug efflux and decreased drug influx, drug inactivation, alterations in drug target, increased DNA damage repair, deregulation of apoptosis, autophagy, activation of prosurvival signalling, oncogenic bypass and pathway redundancy and epithelial–mesenchymal transition (Holohan et al. 2013). The tumour microenvironment has been implicated not only in tumour growth, invasion, and metastasis but also in acquired drug resistance, mediated by myeloid cells, cancer-associated fibroblasts, mesenchymal stem cells and the interaction with the extracellular matrix (Son et al. 2017). Moreover, hypoxia is a common tumour microenvironmental condition that is intimately related to chemoresistance (Semenza 2012; Vaupel and Mayer 2007).

In here, I will focus on some adaptive strategies (inherited or not) that favour drug resistance/tolerance, focusing on metabolic adaptations that allow cancer cells survival upon cytotoxic drugs exposure. It is not my goal to focus on oncogenes, tumour suppressor genes or signalling cascades known to play important roles in the metabolic shifting of cancer cells and on chemoresistance. Instead, it is my goal to explore the role of metabolic reprograming *per se* as a driver of cancer cells adaptation and resistance to anti-cancer drugs.

Albeit the well known role of the Warburg effect on tumorigenesis, its causative effect in chemoresistance is still unclear (Morandi and Indraccolo 2017). Some studies already proposed that targeting glycolysis could be an efficient way to revert both 5-fluorouracil (5-Fu) (Zhao et al. 2014) and doxorubicin (Ma et al. 2015) resistance. Interestingly, Zhao and co-workers have reported that 5-Fu-resistant A549 cells presented an increased glucose metabolism, whereas cisplatin-resistant cells presented a decreased glucose metabolism. In addition, 5-Fu combined with cisplatin contributed to the synergistic anticancer effect through the inhibition of glucose metabolism, suggesting that targeting this metabolic pathway should be effective for overcoming 5-Fu resistance (Zhao et al. 2014). Ma et al. reported an enhanced doxorubicin activity in MCF-7 resistant cells treated with a glucose analogous, 2-deoxy-D-glucose, that inhibits glucose metabolism by competitively inhibiting its uptake and utilization (Ma et al. 2015). This effect on doxorubin reversion of resistance by 2-deoxy-D-glucose was reported to be via intracellular ATP depletion, via the inactivation of drug-efflux pump, and by downregulation of transmembrane transporters (Ma et al. 2015). Zhou et al. have reported that intracellular ATP levels are pivotal in the development of oxaliplatin resistance in human colon cancer cells that present distinct genetic backgrounds (Zhou et al. 2012). The increased ATP levels were shown to be driven by an enhanced aerobic glycolysis in the chemoresistant cells albeit these cells consumed more oxygen without increased mitochondrial ATP production (Zhou et al. 2012). Zhang and colleagues reported that aerobic glycolysis mediated by AMPK/mTOR/HIF1α pathways probably plays a role in resistance to carmustine of mitochondrial hydroxylase Clk1 deficient glioma cells (Zhang et al. 2017a). Moreover, an acidic extracellular environment due to lactate accumulation was also reported to have a role in drug resistance both in vivo and in vitro (reviewed in (Morandi and Indraccolo 2017)). Contrarily to these observations, Pastò and colleagues data suggested that ovarian cancer platinum-sensitive cells (both epithelial ovarian cancer cells from patients and in a xenograft model) rely more on glucose metabolism than their resistant counterparts (Pastò et al. 2017). However, it is unclear if platinum modulates the metabolic shift of cancer cells or if it selects a population of cells that rely less on glucose metabolism (Pastò et al. 2017).

Komurov and colleagues have reported that lapatinib resistance (an epidermal growth factor receptor – EGFR/erb-b2 receptor tyrosine kinase 2 – ErbB2 inhibitor), induced the expression of the glucose deprivation response pathway, including glucagon signalling, glucose uptake and gluconeogenesis (Komurov et al. 2012). They also found that the glucose deprivation pathway was significantly correlated with higher rates of clinical relapse in ErbB2-positive breast cancer patients and that glucose deprivation was able to increase lapatinib-sensitive cells resistance (Komurov et al. 2012). Moreover, they also observed higher glycolysis rates in resistant cells and, since the lactate/glucose ratio was significantly decreased in these cells, they have suggested a switch from glycolysis to the pentose phosphate pathway, leading to increased NADPH and, consequently, to an increased capacity of the resistant cells to overcome oxidative stress (Komurov et al. 2012).

Recently, the hexosamine biosynthetic pathway, which is also involved in glucose metabolism, was reported to play an important role in chemoresistance through the regulation of O-GlcNAcylation in the presence of doxorubicin or camptothecin in several cancer cell lines (Liu et al. 2018). Importantly, the suppression of this pathway or O-GlcNAcylation decreased cancer cells chemoresistance (Liu et al. 2018).

Collectively, data supports an active role of glucose metabolism in the ability of cancer cells to survive upon cytotoxic drugs exposure, weather by favouring it or, on the contrary, by avoiding it, hence favouring other metabolic pathways.

Regarding OXPHOS role on the ability of cancer cells to adapt to anti-cancer drugs, interestingly, Qian and co-workers have shown a posi-

tive correlation between cellular density of mitochondria and cisplatin sensitivity both in vivo and in vitro (Qian et al. 2005). Contrarily, Denise and colleagues have found a mesenchymal stem-like phenotype and an addicted-OXPHOS phenotype in colon cancer cells treated with 5-Fu (Denise et al. 2015). In ovarian cancer, it was shown that chemotherapy treatment induces metabolic plasticity in ovarian cancer stem cells-like recurrent cells, favouring pathways that rely on OXPHOS-mediated lipid metabolism (Ahmed et al. 2018). Ippolito and coworkers have shown that docetaxel treatment induces a glycolytic phenotype shift to an OXPHOS phenotype in resistant prostate cancer cells (Ippolito et al. 2016). Importantly, reverting the OXPHOS phenotype via miR-205 resensitized the resistant cells to docetaxel (Ippolito et al. 2016). These opposite observations strongly supports that the metabolic reprograming causative of drug resistance/tolerance of cancer cells is dependent on the type of chemotherapy agents used (Morandi and Indraccolo 2017). Interestingly, in ovarian cancer context, Dar and colleagues have reported that chemosensitive cancer cell lines presented a glycolytic phenotype whereas the chemoresistant cells exhibited a high metabolically active phenotype, with metabolic switching between OXPHOS and glycolysis (Dar et al. 2017). Importantly, while the chemosensitive cells were glucose-dependent, the chemoresistant ones presented metabolic adaptability (Dar et al. 2017). Moreover, patient derived ovarian cancer cells also presented a similar pattern of chemoresistance, where cells presented a high metabolically active phenotype (Dar et al. 2017). However, the authors could not state if the metabolic adaptation of chemoresistant cells was a driver or an outcome event of chemoresistance (Dar et al. 2017).

It is important to highlight that in cancer, subpopulations of cells with both glycolytic and oxidative metabolisms coexist, providing metabolic plasticity, thus allowing tumour cells survival under different microenvironments, hence possibly supporting tumour metastasis and chemoresistance (Jia et al. 2018). Corroborating this hypothesis, Sancho and co-workers have reported that during metformin exposure, an anti-diabetic drug, the resistant pancreatic cancer stem cells arise with an intermediate glycolytic/respiratory phenotype (Sancho et al. 2015). Moreover, in a very interesting publication, in the context of pancreatic neuroendocrine tumors, Allen and colleagues found that metabolic symbiosis can function as a mechanism of adaptive resistance (Allen et al. 2016). They described this adaptive mechanism in response to anti-angiogenic therapies that lead to hypoxia (Allen et al. 2016). Thus, they have found that hypoxic cancer cells metabolise glucose and secrete lactate, whereas the normoxic cells, which are proximal to the vessels, import and use lactate for energy metabolism, by favouring glutamine metabolism (Allen et al. 2016). Though NMR spectroscopy and using $^{3\text{-}13C}$ lactate in glucose-free media, the authors reported that the normoxic cells catabolised $^{3\text{-}13C}$ lactate to C4-glutamate, C2- and C3-aspartate, and C3-alanine (Allen et al. 2016). Glutamate can be then converted into α-ketoglutarate, replenishing intermediates for the mitochondrial Tricarboxylic acid cycle (TCA) cycle, crucial for energy production and biosynthesis of cellular building blocks (Allen et al. 2016). This publication deeply reflects the enormous complexity involved in the adaptive mechanisms of cancer cells to anti-cancer drugs.

Recently, a role of energy metabolism mediated by miRNAs regulation in chemoresistance was also suggested (reviewed in (Ye et al. 2018)).

Glutamine metabolism was also reported to drive chemoresistance. For instance, Gastel and colleagues have reported the activation of glutamine metabolism as a driver of chemoresistance in in vivo models of acute myeloid leukemia (Gastel et al. 2017). Gallipoli and colleagues have confirmed a role of glutamine metabolism in this disease (Gallipoli et al. 2018). In acute myeloid leukemia, mutations that activate tyrosine kinases (TK) are common and are associated with poor

prognosis, including mutations in the type-III receptor TK fms related tyrosine kinase 3 (FLT3), that frequently result from an internal tandem duplication ($FLT3^{ITD}$) (Gallipoli et al. 2018). Importantly, the authors have reported that following FLT3 inhibition in $FLT3^{ITD}$ cells, glutamine metabolism is protective, allowing an adaptive response to FLT3-TK inhibitors (Gallipoli et al. 2018).

Glutamine is pivotal for several functions in cancer cells, including cellular bioenergetics, nucleotide biosynthesis, and redox homeostasis, as a precursor of glutamate that is used in the synthesis of glutathione (GSH) (reviewed in (Nguyen and Durán 2018)). In fact, another important metabolic adaptation of cancer cells that allows resistance to cytotoxic drugs is the increased cellular antioxidant capacity (Ju et al. 2015; Landriscina et al. 2009). The transcription factor nuclear factor-erythroid 2 p45-related factor 2 (Nrf2) is a pivotal player in cellular redox homeostasis regulation, strongly influencing intrinsic resistance to oxidative stress and controlling adaptive responses to several stressful environmental conditions (Hayes and Dinkova-Kostova 2014). Nrf2 is not only involved in the regulation of the GSH-based antioxidant system, but also regulates the expression of cytosolic thioredoxin (TRX1), TrxR1 and sulphiredoxin1 (Hayes and Dinkova-Kostova 2014). Recently, Khamari and colleagues have shown that the acquisition of B-Raf proto-oncogene, serine/threonine kinase (BRAF) inhibitors resistance was linked with both an increased mitochondrial OXPHOS and with glutamine metabolism (Khamari et al. 2018). They also reported a role of the Nrf2 pathway on melanoma with acquired resistance to BRAF inhibitors, where its strong activation was found to be responsible for an increased pentose phosphate pathway, that is involved in the regeneration of reduced GSH (Khamari et al. 2018). The authors also observed an increased expression of the xCT transporter (Khamari et al. 2018). Thus, they have linked chemoresistance with mitochondrial metabolism adaptations that favour glucose-derived glutamate synthesis, cysteine uptake and GSH synthesis (Khamari et al. 2018), hence strengthening the complex adaptive responses of cancer cells to anti-cancer drugs. Kerr and colleagues found similar metabolic reprogramming features during lung cancer malignant progression in vivo (Kerr et al. 2016). They found that in spontaneous advanced murine lung tumours that present a high frequency of $KRAS^{G12D}$ copy gain, the cells presented a glycolytic switch combined with increased glucose-derived metabolites canalized into the TCA cycle and GSH biosynthesis, leading to an enhanced GSH-mediated detoxification (Kerr et al. 2016). However, this metabolic shifting was not present in the corresponding early tumours ($Kras^{G12D}$ heterozygous). Importantly, the authors also found a plausible role of Nrf2-mediated detoxification in this metabolic switch (Kerr et al. 2016).

An increased antioxidant capacity was also found to contribute to paclitaxel resistance. Hence, Datta and colleagues have shown a gradual increase in GSH content and in the activities of catalase and glutathione peroxidase (GPX) along with paclitaxel resistance development in A549 human lung adenocarcinoma cells (Datta et al. 2017). The authors reported that increased rates of extracellular acidification and oxygen consumption were directly correlated with the acquisition of resistance (Datta et al. 2017).

Strikingly, Roh et al. reported that the inhibition of both GSH and Thioredoxin (Trx) systems presented a synergistic effect on head and neck cancer cells death, but the effect was suboptimal due to the activation of Nrf2-antioxidant response element pathway in resistant cells (Roh et al. 2017). However, with the simultaneously blocking of GSH, Trx and the Nrf2-ARE pathways, the authors were able to eliminate the resistant head and neck cancers (Roh et al. 2017).

Collectively, these results strongly support a key role of both cellular bioenergetics pathways and antioxidant defence systems in cancer biology, thus suggesting that their targeting from an evolutionary perspective could be a successful strategy to fight several types of cancer.

Deblois and co-workers have recently reported that taxane-resistant triple-negative breast cancer cells endure metabolic adaptations by impairing methionine metabolism and S-adenosylmethionine availability, leading to a

global decrease in DNA methylation that H3K27me3 forming large organized chromatin domains of lysine modification compensate (Deblois et al. 2018). Moreover, this epigenetic reprogramming induced by metabolic adaptations, lead to an epigenetic-targeted opportunity to re-sensitize the taxane-resistant cells with chemical inhibitors of EZH2, the H3K27me3 methyltransferase (Deblois et al. 2018). Hence, this work has shown the vast possible complex consequences of metabolism alterations in epigenetics reprograming and drug resistance.

The goal of this section was to illustrate the complexity involved in the metabolic adaptive strategies that cancer cells undergo allowing their survival upon exposure to anti-cancer drugs. In the next section, the relevance of evolutionary principles in preventing the spread of chemoresistant phenotypes will be explored. These strategies could, therefore, counteract the emergency of these metabolic adaptive strategies in cancer cells, culminating possibly in the overcome of drug-resistance/tolerance.

15.4 Turning Cancer Cells Adaptability Against Themselves: The Power of Evolutionary Strategies in Overcoming Chemoresistance

In the previous section, several examples of active metabolism reprogramming as a causative effect of cancer cells adaptation to anti-cancer drugs were presented. The link with the development of metabolic pathways-targeting drugs is then obvious, but I do not intend to explore the drugs that were already developed following this rational. Instead, given the role of adaptive evolution in cancer cells resistance/tolerance to treatment, it is my objective to address the treatment strategies that exploit the dynamics of cancer cells adaptation to anti-cancer drugs. The ultimate goal of these strategies is, therefore, to prevent the possibility of cancer cells to adapt to anti-cancer drugs, regardless the adaptive mechanism. In the next sections, some of the different evolutionary perspectives that were already explored in cancer research will be addressed, namely the adaptive therapy and the fitness threshold model. Other perspectives will be also discussed.

15.4.1 Exploiting the Cost of Resistance: Playing with the Ecology of Cancer Cells

It is important to highlight that the conventional cancer therapies, which administer cytotoxic drugs at maximum tolerated doses until progression, strongly select for resistant phenotypes and, by eliminating the sensitive cells, eliminate competition, allowing a rapid proliferation of the resistant populations even in the absence of drugs – an evolutionary phenomenon designated "competitive release" (Enriquez-navas et al. 2015; Enriquez-Navas et al. 2016; Zhang et al. 2017a, b). However, as more and more evidence accumulates highlighting cancer as an evolutionary disease, in 2011, Atkipis et al. analysed 6228 publications concerning therapeutic resistance and/or cancer relapse and reported that in abstracts, evolution terms were present in only about 1% since the 1980s (Aktipis et al. 2011). Moreover, Darwinian dynamics are still rarely integrated into anti-cancer protocols in clinical contexts (Zhang et al. 2017b).

In 2009, Gatenby and colleagues have explored the conceptual model of adaptive therapy that defends that, since the tumour populations that are exposed to treatment are dynamic, the treatment should be also dynamic with continuous adjustment of drugs, dose, and timing (Gatenby et al. 2009), thus evolving along with cancer cells. The authors have developed mathematical models that predicted that an optimal treatment strategy adjust therapy in order to maintain a stable population of chemosensitive cells that are more fitted in the absence of therapy, being able to compete and inhibit the growth of resistant populations due to fitness costs of resistance (Fig. 15.1) (Gatenby et al. 2009). The same authors confirmed the benefits of the adaptive therapy in in vivo experiments with OVCAR3

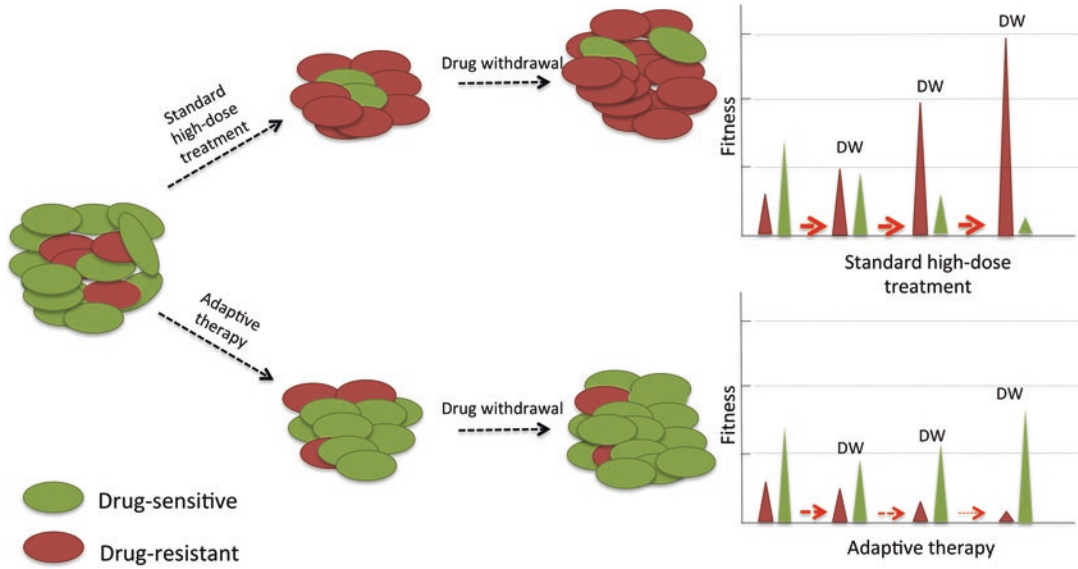

Fig. 15.1 The power of adaptive therapy in maintaining a stable tumour population, by playing with competition among resistant and sensitive cells
The standard high-dose treatment strongly selects resistant phenotypes by eliminating the sensitive cells that competes with the resistant cells, allowing the rapid spread of resistant cells even in the absence of drugs. Hence, albeit an initial tumour shrinkage can be observed, this tumour is mainly composed by resistant cells that gain fitness during treatment, even in the absence of the drug (upper panel). On the contrary, by administering lower doses with continuous adjustments, the resistant cells undergo competition with sensitive cells, allowing the maintenance of a stable tumour population for a prolonged period of time, hence maintaining the resistant cells with a constant lower fitness. The red arrows correspond to the treatment administration, where the width reflects the dose used during treatment and DW to drug withdrawal. (Adapted from Enriquez-Navas and Gatenby 2017 and Salgia and Kulkarni 2018)

xenografts treated with carboplatin, showing that this sstrategy was able to maintain a stable tumour population for a prolonged period of time, allowing a long-term survival (Gatenby et al. 2009). Enriquez-Navas and colleagues reported similar findings in different preclinical models of breast cancer using paclitaxel (Enriquez-Navas et al. 2016). Gallaher et al. went further and identified two different adaptive strategies that are effective in heterogeneous tumours, a dose modulation strategy that is efficient in the majority of tumours with fewer drug, and a more vacation-oriented strategy that is able to control more invasive tumours (Gallaher et al. 2017). Importantly, Silva and colleagues have reported that low doses of verapamil and 2-deoxyglucose, were able to increase the cost of resistance and to decrease energy production, abolishing drug-resistant cells proliferation in vivo (Silva et al. 2012). In breast cancer tumour models, this strategy allowed to increase the time to progression by 2- to ten-fold compared to standard high dose treatments (Silva et al. 2012). Hence, these authors have shown that these evolutionary strategies are also effective when targeting metabolic pathways of cancer cells.

Recently, Zhang and colleagues have integrated evolutionary dynamics into a pilot clinical trial of patients with metastatic castrate-resistant prostate cancer in order to avoid the evolution of resistance to abiraterone (that inhibits CYP17A, an enzyme responsible for testosterone auto-production). Outstandingly, the authors have reported that the adaptive therapy treatment was able to increase the time to progression and to reduce the cumulative drug dose to less than a half compared to the standard strategy (Zhang et al. 2017b).

The cost of resistance in the absence of drugs was also explored in a different perspective, as

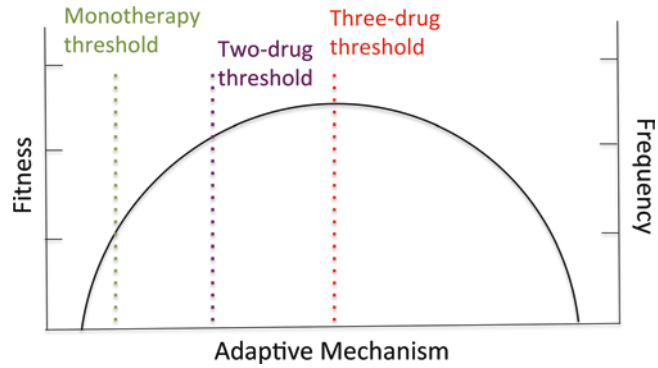

Fig. 15.2 The fitness threshold model as a tool to prevent the emergency of resistance
In accordance with this model, the fitness threshold corresponds to the barrier that subclonal populations need to overcome in order to recover fitness during drug treatment (Xue et al. 2017). The model predicted that, whereas the sequential treatment with RAF inhibitor followed by an ERK inhibitor was not effective, an intermittent three-drug treatment combination was, allowing the increase of the fitness threshold and counteracting the adaptive mechanisms of cancer cells (Xue et al. 2017). This approach could be possibly used to counteract other types of adaptive mechanisms beyond BRAF copy number gain with different anti-cancer drugs, when both the monotherapy and a two-drug combination are not effective. (Adapted from Xue et al. 2017)

chemoresistance may induce drug addiction due to the high fitness costs upon drug withdrawal. Therefore, drug addiction is the dependency of tumour cells on the anti-cancer drugs to which they have developed resistance (Kong et al. 2017), that may allow clinical benefits. In the context of melanoma, Kong and colleagues observed that even after an extended drug withdrawal, resistant clones could arise (Kong et al. 2017), thus, surpassing the drug addicted phenotype. Therefore, in a patient setting, they combined the drug withdrawal of BRAF inhibition with the introduction of dacarbazine, an alkylating agent generally used as a monotherapy in metastatic melanoma, even with poor response rates (Kong et al. 2017). Whereas dacarbazine showed low cytotoxic effects in the presence of BRAF inhibitor on melanoma cell lines, the administration of dacarbazine upon BRAF inhibitor withdrawal presented a strong synergetic effect (Kong et al. 2017). The authors argued that gaining insights into the molecular mechanisms of drug addiction may open the opportunity to develop alternating more efficient treatment strategies in order to fight chemoresistance (Kong et al. 2017).

Together, growing evidence had strengthened the use of evolutionary principles in clinical settings as an efficient and powerful way to prevent the spread of chemoresistant phenotypes. These studies have also shown that from identical evolutionary points of view (e.g. the cost of resistance in the absence of the drug), different evolutionary strategies may be developed. Moreover, evidence also support that these principles are effective for several types of anti-cancer drugs and in several cancer contexts, hence supporting its general use in cancer management.

15.4.2 The Fitness Threshold Model and Beyond

In a different evolutionary perspective, by using single-cell DNA sequencing, Xue and colleagues have found that parallel evolution lead to the selection and spread of different *BRAF*-amplified subclones, allowing the tumours to adapt to ERK inhibitor treatment while maintaining intratumoral heterogeneity (Xue et al. 2017). They proposed the fitness threshold model (Fig. 15.2) to explain their findings, being the fitness threshold the barrier that subclonal populations have to overcome in order to recover fitness during drug treatment. The model predicted that sequential treatment was not effective, prediction that was

supported by their results showing that treatment with a RAF inhibitor followed by an ERK inhibitor induced a gradual increase in *BRAF* copy number, allowing a fitness advantage in the presence of the drugs (Xue et al. 2017). Moreover, the same authors reported that an intermittent three-drug treatment combination was able to inhibit tumour growth in $BRAF^{V600E}$ patient-derived tumour xenografts models for lung cancer and melanoma, hence being able to increase the fitness threshold and counteracting the spread of subclones with *BRAF*-amplification (Xue et al. 2017). However, the authors did not address the hypothesis of resistance emergency with the intermittent three-drug treatment combination and, if so, if other alternative treatments would be plausible.

Noticeably, Xue and colleagues have tested different scenarios of drugs administration, including the continuous versus intermittent administration and also different sequences of drug administration (Xue et al. 2017). However, in their model, a lower efficiency of regimens in which the drugs were not given simultaneously was found (Xue et al. 2017).

The idea that therapy response is dependent on the sequence of administration of anti-cancer drugs is gaining prominence (Goldman et al. 2015). Goldman reported that the administration of a chemotherapy drug pair in a specific temporal sequence was able to surpass the adaptive resistance by targeting a vulnerable drug-induced phenotypic transition (Goldman et al. 2015). They found that the treatment of breast cancer cells with Src Family Kinase inhibitors after a taxane-based treatment, but not the co-administration, significantly sensitised the cells to the treatment, resulting in an enhanced anti-cancer outcome (Goldman et al. 2015). This is in accordance with Kent and Green that reported that the order in which genetic mutations arise impacts cancer evolution (Kent and Green 2017). Moreover, the case study reported by Shaw and colleagues truly reflects the power of drug sequence in therapy outcome, by describing the dynamics of response to lorlatinib and crizotinib in a non–small-cell lung cancer patient (Shaw et al. 2016).

In a different evolutionary perspective, Niekerk and colleagues have defended the clinical relevance of synthetic lethality (meaning that the concurrent loss of function in two genes results in lethality, whereas the loss of function in each single gene is tolerated due to compensatory effects) in the context of cancer (van Niekerk et al. 2017). The authors argued that cancer cells are subject to evolutionary trajectories selecting for functional dependencies similar to synthetic lethality, being the auxotrophic induction a way to "turn the evolvability of cancer cells against themselves" (van Niekerk et al. 2017). In fact, evidence suggests that cancer cells display evolution of auxotrophic phenotypes, such as auxotrophy toward arginine or the "oncogene addiction" (van Niekerk et al. 2017).

Noticeably, Russo and colleagues have reported the simultaneously emergence of different acquired resistance mechanisms in separate metastases within the same colorectal cancer patient, leading to diverse responses to the following targeted therapies (Russo et al. 2016). This observation strengthens the pivotal role of evolutionary strategies in the clinical settings, as these could help to trace alternative effective strategies, by "playing" with the different adaptive/resistance mechanisms present in the different metastases within the same individual.

Importantly, Sun and colleagues performed a systematic computational analysis in order to address the effects of different drug-imposed selective pressures on long-term therapeutic outcomes of cancer cells (Sun et al. 2016). They observed that the initial tumour response may not be the best prognosis predictor, since when the initial selective pressure imposed by the drug was identical (meaning an identical cells eradication), different therapeutic outcomes were observed due to differential selective pressure on the subpopulations of cells (Sun et al. 2016). Moreover, their findings were corroborated with a preclinical murine model of Burkitt's lymphoma (Sun et al. 2016). Importantly, they reported the existence of an intrinsic trade-off in maximizing overall tumour cells killing and a higher resistance potential, hence showing that the traditional

chemotherapy regimens may lead to tumour shrinkage at the cost of drug sensitivity (Sun et al. 2016).

Taken together, evidence strongly supports the use of evolutionary principles in several and diverse ways in the clinical context of cancer. Clinical protocols that join evolutionary dynamics of cancer cells response to therapy should be of extreme importance as it would possibly allow not only to predict the emergence of resistance, but also to overcome it, hence allowing to change the outcome of this complex group of diseases. These clinical evolutionary strategies could then counteract the evolution of the adaptive strategies of cancer cells, such as metabolic reprograming, hence allowing to overcome drug resistance/tolerance, probably impacting profoundly cancer outcome.

15.5 Final Remarks

More and more evidence supports that cancer cells exhibit metabolic plasticity that enables their survival in changing and challenging environments. Recently, this metabolic plasticity of cancer cells has been found to be itself a driver of chemoresistance. Hence, the knowledge of these metabolic adaptations should be of extreme importance for disease outcome, as more efficient strategy treatments could be developed. More than developing new drugs that target these metabolic adaptations directly, treatments that exploit the evolutionary dynamics of cancer cells response and adaptation to anti-cancer drugs may allow the avoidance of chemoresistance emergency and spread, possibly by preventing these same metabolic adaptations. These evolutionary principles were found to be effective in several cancer types and with several types of drugs, hence opening the opportunity to develop general evolution-guided protocols with drugs that are already used in the clinical setting. This also opens the opportunity to rethink the way anti-cancer drugs are being administered, the dose used, its schedule and the sequence of the drugs that are used, details that may impact profoundly the disease outcome. Trying to avoid the adaptability and evolvability of cancer cells is only possible if the treatments also evolve along with cancer cells. This would ultimately allow to predict and to overcome chemoresistance, changing cancer prognosis.

Acknowledgments The authors acknowledge iNOVA-4Health – UID/Multi/04462/2013, a program financially supported by Fundação para a Ciência e Tecnologia/Ministério da Educação e Ciência, through national funds and co-funded by FEDER under the PT2020 Partnership Agreement.

References

Ahmed N, Escalona R, Leung D, Chan E, Kannourakis G (2018) Tumour microenvironment and metabolic plasticity in cancer and cancer stem cells: perspectives on metabolic and immune regulatory signatures in chemoresistant ovarian cancer stem cells. Semin Cancer Biol 53:265–281. https://doi.org/10.1016/J.SEMCANCER.2018.10.002

Aktipis CA, Kwan VSY, Johnson KA, Neuberg SL, Maley CC (2011) Overlooking evolution: a systematic analysis of cancer relapse and therapeutic resistance research. PLoS One 6:e26100.1–e26100.9. https://doi.org/10.1371/journal.pone.0026100

Alam MM, Lal S, FitzGerald KE, Zhang L (2016) A holistic view of cancer bioenergetics: mitochondrial function and respiration play fundamental roles in the development and progression of diverse tumors. Clin Transl Med 5(3). https://doi.org/10.1186/s40169-016-0082-9

Allen E, Ville PM, Warren CM, Saghafinia S, Li L, Peng MW, Hanahan D (2016) Metabolic symbiosis enables adaptive resistance to anti-angiogenic therapy that is dependent on mTOR signaling. Cell Rep 15:1144–1160. https://doi.org/10.1016/j.celrep.2016.04.029

Axelrod R, Axelrod DE, Pienta KJ (2006) Evolution of cooperation among tumor cells. Proc Natl Acad Sci U S A 103:13474–13479. https://doi.org/10.1073/pnas.0606053103

Cairns J (1975) Mutation selection and the natural history of cancer. Nature 255:197–200. https://doi.org/10.1038/255197a0. https://www.cancerresearchuk.org/ (2018)

Crespi B, Summers K (2005) Evolutionary biology of cancer. Trends Ecol Evol 20:545–552. https://doi.org/10.1016/j.tree.2005.07.007

Dar S, Chhina J, Mert I, Chitale D, Buekers T, Kaur H et al (2017) Bioenergetic adaptations in chemoresistant ovarian cancer cells. Sci Rep 7:1–17. https://doi.org/10.1038/s41598-017-09206-0

Datta S, Choudhury D, Das A, Das Mukherjee D, Das N, Roy SS, Chakrabarti G (2017) Paclitaxel resistance development is associated with biphasic

changes in reactive oxygen species, mitochondrial membrane potential and autophagy with elevated energy production capacity in lung cancer cells: a chronological study. Tumor Biol 39:1–14. https://doi.org/10.1177/1010428317694314

Deblois G, Tonekaboni SAM, Kao YI, Tai F, Liu X, Ettayebi I et al (2018) Metabolic adaptations underlie epigenetic vulnerabilities in chemoresistant breast cancer. bioRxiv:1–51. https://doi.org/10.1101/286054

Denise C, Paoli P, Calvani M, Taddei ML, Giannoni E, Kopetz S et al (2015) 5-fluorouracil resistant colon cancer cells are addicted to OXPHOS to survive and enhance stem-like traits. Oncotarget 6:41706–41721. https://doi.org/10.18632/oncotarget.5991

Enriquez-navas PM, and Gatenby RA (2017) Applying tools from evolutionary biology to cancer research. Ecol Evol Cancer. Chapter 14:193–200. https://doi.org/10.1016/B978-0-12-804310-3/00014-4

Enriquez-navas PM, Wojtkowiak JW, Gatenby RA (2015) Application of evolutionary principles to cancer therapy. Cancer Res 75:4675–4680. https://doi.org/10.1158/0008-5472.CAN-15-1337

Enriquez-Navas PM, Kam Y, Das T, Hassan S, Silva A, Foroutan P et al (2016) Exploiting evolutionary principles to prolong tumor control in preclinical models of breast cancer. Sci Transl Med 8:1–9. https://doi.org/10.1126/scitranslmed.aad7842

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C et al. (2013a) GLOBOCAN 2012a v1.0, cancer incidence and mortality worldwide: IARC cancerbase No. 11. Retrieved August 24, 2018, from http://globocan.iarc.fr

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C et al. (2013b) GLOBOCAN 2012b v1.0, cancer incidence and mortality worldwide: IARC cancerbase no. 11. Retrieved August 30, 2018, from http://globocan.iarc.fr

Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF et al (2015) The global burden of cancer 2013. JAMA Oncol 1:505–527. https://doi.org/10.1001/jamaoncol.2015.0735

Gallaher JA, Enriquez-Navas PM, Luddy KA, Gatenby RA, Anderson ARA (2017) Spatial heterogeneity and evolutionary dynamics modulate time to recurrence in continuous and adaptive cancer therapies. bioRxiv:1–21. https://doi.org/10.1101/128959

Gallipoli P, Giotopoulos G, Tzelepis K, Costa ASH, Vohra S, Medina-Perez P et al (2018) Glutaminolysis is a metabolic dependency in FLT3ITDacute myeloid leukemia unmasked by FLT3 tyrosine kinase inhibition. Blood 131:1639–1653. https://doi.org/10.1182/blood-2017-12-820035

Gastel N, van Schajnovitz A, Vidoudez C, Oki T, Sharda A, Trauger SA, Scadden DT (2017) Untargeted metabolomics identifies glutamine metabolism as a driver of chemoresistance in acute myeloid Leukemia. Blood 130:2523

Gatenby RA, Silva AS, Gillies RJ, Frieden BR (2009) Adaptive therapy. Cancer Res 69:4894–4903. https://doi.org/10.1158/0008-5472.CAN-08-3658

Gillies RJ, Verduzco D, Gatenby RA (2012) Evolutionary dynamics of carcinogenesis and why targeted therapy does not work. Nat Rev Cancer 12:487–493. https://doi.org/10.1038/nrc3298

Goldman A, Majumder B, Dhawan A, Ravi S, Goldman D, Kohandel M et al (2015) Temporally sequenced anticancer drugs overcome adaptive resistance by targeting a vulnerable chemotherapy-induced phenotypic transition. Nat Commun 6:1–13. https://doi.org/10.1038/ncomms7139

Gottesman MM (2002) Mechanisms of cancer drug resistance. Annu Rev Med 53:615–627. https://doi.org/10.1146/annurev.med.53.082901.103929

Guppy M, Leedman P, Zu X, Russell V (2002) Contribution by different fuels and metabolic pathways to the total ATP turnover of proliferating MCF-7 breast cancer cells. Biochem J 364:309–315. https://doi.org/10.1042/bj3640309

Hanahan D, Weinberg RA (2000) The hallmarks of cancer. Cell 100:57–70. https://doi.org/10.1007/s00262-010-0968-0

Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144:646–674. https://doi.org/10.1016/j.cell.2011.02.013

Hayes JD, Dinkova-Kostova AT (2014) The Nrf2 regulatory network provides an interface between redox and intermediary metabolism. Trends Biochem Sci 39:199–218. https://doi.org/10.1016/j.tibs.2014.02.002

Holohan C, Van Schaeybroeck S, Longley DB, Johnston PG (2013) Cancer drug resistance: an evolving paradigm. Nat Rev Cancer 13:714–726. https://doi.org/10.1038/nrc3599

Ippolito L, Marini A, Cavallini L, Morandi A, Pietrovito L, Pintus G et al (2016) Metabolic shift toward oxidative phosphorylation in docetaxel resistant prostate cancer cells. Oncotarget 7:61890–61904. https://doi.org/10.18632/oncotarget.11301

Jia D, Park J, Jung K, Levine H, Kaipparettu B (2018) Elucidating the metabolic plasticity of cancer: mitochondrial reprogramming and hybrid metabolic states. Cell 7:21. https://doi.org/10.3390/cells7030021

Ju HQ, Gocho T, Aguilar M, Wu M, Zhuang ZN, Fu J et al (2015) Mechanisms of overcoming intrinsic resistance to gemcitabine in pancreatic ductal adenocarcinoma through the redox modulation. Mol Cancer Ther 14:788–798. https://doi.org/10.1158/1535-7163.MCT-14-0420

Kent DG, Green AR (2017) Order matters: the order of somatic mutations influences cancer evolution. Cold Spring Harb Perspect Med 7:1–16. https://doi.org/10.1101/cshperspect.a027060

Kerr EM, Gaude E, Turrell FK, Frezza C, Martins CP (2016) Mutant Kras copy number defines metabolic reprogramming and therapeutic susceptibilities. Nature 531:110–113. https://doi.org/10.1038/nature16967

Khamari R, Trinh A, Gabert PE, Corazao-Rozas P, Riveros-Cruz S, Balayssac S et al (2018) Glucose metabolism and NRF2 coordinate the antioxidant response in melanoma resistant to MAPK inhibitors.

Cell Death Dis 9:325–338. https://doi.org/10.1038/s41419-018-0340-4

Komurov K, Tseng JT, Muller M, Seviour EG, Moss TJ, Yang L et al (2012) The glucose-deprivation network counteracts lapatinib-induced toxicity in resistant ErbB2-positive breast cancer cells. Mol Syst Biol 8:1–10. https://doi.org/10.1038/msb.2012.25

Kong X, Kuilman T, Shahrabi A, Boshuizen J, Kemper K, Song JY et al (2017) Cancer drug addiction is relayed by an ERK2-dependent phenotype switch. Nature 550:270–274. https://doi.org/10.1038/nature24037

Landriscina M, Maddalena F, Laudiero G, Esposito F (2009) Adaptation to oxidative stress, chemoresistance, and cell survival. Antioxid Redox Signal 11:2701–2716. https://doi.org/10.1089/ars.2009.2692

Liang C, Qin Y, Zhang B, Ji S, Shi S, Xu W et al (2017) ARF6, induced by mutant Kras, promotes proliferation and Warburg effect in pancreatic cancer. Cancer Lett 388:303–311. https://doi.org/10.1016/j.canlet.2016.12.014

Liberti MV, Locasale JW (2016) The Warburg effect: how does it benefit cancer cells? Trends Biochem Sci 41:211–218. https://doi.org/10.1016/j.tibs.2015.12.001

Liu T, Yin H (2017) PDK1 promotes tumor cell proliferation and migration by enhancing the Warburg effect in non-small cell lung cancer. Oncol Rep 37:193–200. https://doi.org/10.3892/or.2016.5253

Liu Y, Cao Y, Pan X, Shi M, Wu Q, Huang T et al (2018) O-GlcNAc elevation through activation of the hexosamine biosynthetic pathway enhances cancer cell chemoresistance. Cell Death Dis 9:485–496. https://doi.org/10.1038/s41419-018-0522-0

Lopes-Coelho F, Nunes C, Gouveia-Fernandes S, Rosas R, Silva F, Gameiro P et al (2017) Monocarboxylate transporter 1 (MCT1), a tool to stratify acute myeloid leukemia (AML) patients and a vehicle to kill cancer cells. Oncotarget 8:82803–82823. https://doi.org/10.18632/oncotarget.20294

Ma S, Jia R, Li D, Shen B (2015) Targeting cellular metabolism chemosensitizes the doxorubicin-resistant human breast adenocarcinoma cells. Biomed Res Int 2015:1–8. https://doi.org/10.1155/2015/453986

Maley CC, Aktipis A, Graham TA, Sottoriva A, Boddy AM, Janiszewska M et al (2017) Classifying the evolutionary and ecological features of neoplasms. Nat Rev Cancer 17:605–619. https://doi.org/10.1038/nrc.2017.69

Merlo LMF, Pepper JW, Reid BJ, Maley CC (2006) Cancer as an evolutionary and ecological process. Nat Rev Cancer 6:924–935. https://doi.org/10.1038/nrc2013

Morandi A, Indraccolo S (2017) Linking metabolic reprogramming to therapy resistance in cancer. Biochimica et Biophysica Acta – Rev Cancer 1868:1–6. https://doi.org/10.1016/j.bbcan.2016.12.004

Nguyen TL, Durán RV (2018) Glutamine metabolism in cancer therapy. Cancer Drug Resist 1:126–138. https://doi.org/10.20517/cdr.2018.08

Nowell PC (1976) The clonal evolution of tumor cell populations. Science 194:23–28. https://doi.org/10.1126/science.191.4224.241-a

Pastò A, Pagotto A, Pilotto G, De Paoli A, De Salvo GL, Baldoni A et al (2017) Resistance to glucose starvation as metabolic trait of platinum- resistant human epithelial ovarian cancer cells. Oncotarget 8:6433–6445. https://doi.org/10.18632/oncotarget.14118

Polyak K (2007) Breast cancer stem cells: a case of mistaken identity? Stem Cell Rev 3:107–109. https://doi.org/10.1007/s12015-007-0020-8

Qian W, Nishikawa M, Haque AM, Hirose M, Mashimo M, Sato E, Inoue M (2005) Mitochondrial density determines the cellular sensitivity to cisplatin-induced cell death. Am J Phys Cell Phys 289:C1466–C1475. https://doi.org/10.1152/ajpcell.00265.2005

Rankin EB, Giaccia AJ (2016) Hypoxic control of metastasis. Science 352:175–180. https://doi.org/10.1126/science.aaf4405

Rodríguez-Enríquez S, Torres-Márquez ME, Moreno-Sánchez R (2000) Substrate oxidation and ATP supply in AS-30D hepatoma cells. Arch Biochem Biophys 375:21–30. https://doi.org/10.1006/abbi.1999.1582

Rodríguez-Enríquez S, Vital-González PA, Flores-Rodríguez FL, Marín-Hernández A, Ruiz-Azuara L, Moreno-Sánchez R (2006) Control of cellular proliferation by modulation of oxidative phosphorylation in human and rodent fast-growing tumor cells. Toxicol Appl Pharmacol 215:208–217. https://doi.org/10.1016/j.taap.2006.02.005

Roh JL, Jang H, Kim EH, Shin D (2017) Targeting of the glutathione, thioredoxin, and Nrf2 antioxidant systems in head and neck cancer. Antioxid Redox Signal 27:106–114. https://doi.org/10.1089/ars.2016.6841

Russo M, Siravegna G, Blaszkowsky LS, Corti G, Crisafulli G, Ahronian LG et al (2016) Tumor heterogeneity and lesion-specific response to targeted therapy in colorectal cancer. Cancer Discov 6:147–153. https://doi.org/10.1158/2159-8290.CD-15-1283

Salgia R, Kulkarni P (2018) The genetic/non-genetic duality of drug "resistance" in cancer. Trends Cancer 4:110–118. https://doi.org/10.1016/j.trecan.2018.01.001

Sancho P, Burgos-Ramos E, Tavera A, Bou Kheir T, Jagust P, Schoenhals M et al (2015) MYC/PGC-1α balance determines the metabolic phenotype and plasticity of pancreatic cancer stem cells. Cell Metab 22:590–605. https://doi.org/10.1016/j.cmet.2015.08.015

Semenza GL (2012) Hypoxia-inducible factors: mediators of cancer progression and targets for cancer therapy. Trends Pharmacol Sci 33:207–214. https://doi.org/10.1016/j.tips.2012.01.005

Shaw AT, Friboulet L, Leshchiner I, Gainor JF, Bergqvist S, Brooun A et al (2016) Resensitization to crizotinib by the lorlatinib ALK resistance mutation L1198F. N Engl J Med 374:54–61. https://doi.org/10.1038/nrg3575.Systems

Silva AS, Kam Y, Khin ZP, Minton SE, Gillies RJ, Gatenby RA (2012) Evolutionary approaches to prolong progression-free survival in breast cancer.

Cancer Res 72:6362–6370. https://doi.org/10.1002/bmb.20244.DNA

Son B, Lee S, Youn H, Kim E, Kim W, Youn B (2017) The role of tumor microenvironment in therapeutic resistance. Oncotarget 8:3933–3945. https://doi.org/10.18632/oncotarget.13907

Sun D, Dalin S, Hemann MT, Lauffenburger DA, Zhao B (2016) Differential selective pressure alters rate of drug resistance acquisition in heterogeneous tumor populations. Sci Rep 6:1–13. https://doi.org/10.1038/srep36198

Swanton C (2013) Intratumour heterogeneity : evolution through space and time an evolutionary perspective on cancer heterogeneity. Cancer Res 72:4875–4882. https://doi.org/10.1158/0008-5472.CAN-12-2217. Intratumour

van Niekerk G, Nell T, Engelbrecht AM (2017) Domesticating cancer: an evolutionary strategy in the war on Cancer. Front Oncol 7:1–8. https://doi.org/10.3389/fonc.2017.00304

Vaupel P, Mayer A (2007) Hypoxia in cancer: significance and impact on clinical outcome. Cancer Metastasis Rev 26:225–239. https://doi.org/10.1007/s10555-007-9055-1

Viale A, Corti D, Draetta GF (2015) Tumors and mitochondrial respiration: a neglected connection. Cancer Res 75:1–5. https://doi.org/10.1158/0008-5472.CAN-15-0491

Warburg O (1956) On the origin of cancer cells on the origin of cancer. Science 123:309–314. https://doi.org/10.1126/science.123.3191.309

Xue Y, Martelotto L, Baslan T, Vides A, Solomon M, Mai TT et al (2017) An approach to suppress the evolution of resistance in BRAF V600E-mutant cancer. Nat Med 23:929–937. https://doi.org/10.1038/nm.4369

Ye J, Zou M, Li P, Liu H (2018) MicroRNA regulation of energy metabolism to induce chemoresistance in cancers. Technol Cancer Res Treat 17:1–6. https://doi.org/10.1177/1533033818805997

Yu L, Lu M, Jia D, Ma J, Ben-Jacob E, Levine H et al (2017) Modeling the genetic regulation of cancer metabolism: interplay between glycolysis and oxidative phosphorylation. Cancer Res 77:1564–1574. https://doi.org/10.1158/0008-5472.CAN-16-2074. Modeling

Zhang L, Yang H, Zhang W, Liang Z, Huang Q, Guoqiang X et al (2017a) Clk1–regulated aerobic glycolysis is involved in gliomas chemoresistance. J Neurochem 142:574–588. https://doi.org/10.1111/ijlh.12426

Zhang J, Cunningham JJ, Brown JS, Gatenby RA (2017b) Integrating evolutionary dynamics into treatment of metastatic castrate-resistant prostate cancer. Nat Commun 8:1–9. https://doi.org/10.1038/s41467-017-01968-5

Zhao JG, Ren KM, Tang J (2014) Overcoming 5-Fu resistance in human non-small cell lung cancer cells by the combination of 5-Fu and cisplatin through the inhibition of glucose metabolism. Tumor Biol 35:12305–12315. https://doi.org/10.11862/CJIC.2015.154

Zhou Y, Tozzi F, Chen J, Fan F, Xia L, Wang J et al (2012) Intracellular ATP levels are a pivotal determinant of chemoresistance in colon cancer cells. Cancer Res 72:304–314. https://doi.org/10.1158/0008-5472.CAN-11-1674