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CANCER METABOLIC PROGRAMMING & INNOVATIVE APPROACH TO OVERCOMES RESISTANCE AND TOXICITY OF ANTI-CANCER DRUG

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ABSTRACT

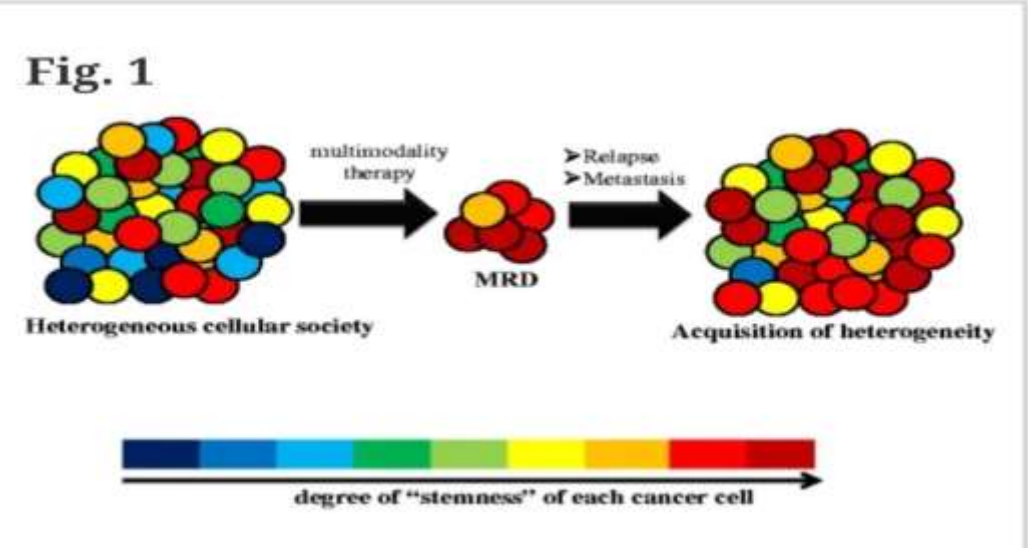
Cancer cells are well documented to rewire their metabolism and energy production networks to support and enable rapid proliferation, continuous growth, survival in harsh conditions, invasion, metastasis, and resistance to cancer treatments. Since Dr. Otto Warburg's discovery about altered cancer cell metabolism in 1930, thousands of studies have shed light on various aspects of cancer metabolism with a common goal to find new ways for effectively eliminating tumor cells by targeting their energy metabolism. This review highlights the importance of the main features of cancer metabolism, summarizes recent remarkable advances in this field, and points out the potentials to translate these scientific findings into life-saving diagnosis and therapies to help cancer patients. Every year, cancer is responsible for millions of deaths worldwide and, even though much progress Has been achieved in medicine, there are still many issues that must be addressed in order to Improve cancer therapy. For this reason, oncological research is putting a lot of effort towards finding New and efficient therapies which can alleviate critical side effects caused by conventional Treatments. Different technologies are currently under evaluation in clinical trials or have been Already introduced into clinical practice. While nanomedicine is contributing to the development of Biocompatible materials both for diagnostic and therapeutic purposes, bioengineering of Extracellular vesicles and cells derived from patients has allowed designing ad hoc systems and Univocal targeting strategies. In this review, we will provide an indepth analysis of the most Innovative advances in basic and applied cancer research.

KEYWORDS: Cell cycle, energy metabolism, glycolysis, glutaminolysis, mitochondria cancer, nanomedicine, extracellular vesicles, targeted therapy, immunotherapy, gene Therapy, thermal ablation, radiomics, pathomics.

INTRODUCTION

Tumor tissue consists of a heterogeneous cellular population. Stromal cells such as neurons, vascular endothelial cells, fibroblasts, and macrophages in cancer tissue drive chemotherapy resistance[1] as well as tumor survival and progression.[2,3] Even in pure populations of tumor cells, heterogeneity is present as a result of genetic mutation and epigenetic modulations. This cellular heterogeneity can be explained by a hierarchical model, in which cancer stem-like cells (CSCs) can provide transient amplifying cells and differentiated non-CSCs involved in establishing the tumor tissue.[4,5] CSCs possess several biological features of "stemness", a combination of phenotypes including plasticity in the transition between quiescent (G_0 phase) and proliferative states[6] and resistance to redox stress and chemotherapeutic agents.[7,8] Importantly, accumulating evidence suggests that metabolic reprogramming is crucial in order for CSCs to maintain unlimited self-renewal potential and hyper-adaptation to drastic changes in the tumor microenvironment.[9–11]

Intra-tumoral heterogeneity due to the presence of CSCs is primarily responsible for our inability to induce the same therapeutic effect among cancer cells as a whole.[12,13] CSCs are very likely to contribute to the formation of minimal residual disease (MRD).[1] The term 'MRD' is most often used in the context of hematological malignant disorders[14], but the underlying concept is quite convenient in discussion of clinically undetectable resistant clones after conventional anti-tumor therapies.[1] Thus, MRD is expected to contribute prominently to latent relapse and distant metastasis (Fig. 1). Cells characterised by different molecular features and diverse responsivity to therapies. This Heterogeneity can be appreciated both at spatial and temporal levels and is the key factor Responsible for the development of resistant phenotypes promoted by a selective pressure upon Treatment administration.



(Fig.1)

Cancer stem cells and MRD formation. Heterogeneous tumor tissue with combined-modality therapy leads to the formation of MRD, which is clinically undetectable. Transiently reduced heterogeneity is observed in MRD, which is enriched in CSCs. Relapse or metastasis results in re-acquisition of a heterogeneous population that is more potentially aggressive in terms of its degree of "stemness"

Aberrant proliferation of cancer cells is supported by enhanced adaptation to nutrient microenvironment mediated by alterations in energy metabolism. Consequently, metabolic reprogramming is believed to be one of the hallmarks of tumor cells in parallel with genomic instability, tumor-provoking chronic inflammation, escape from the immune system, etc.[5] Although aerobic glycolysis, termed the Warburg effect, is a characteristic metabolic feature of cancer cells[15,16], recent investigations revealed that other metabolic features, in particular, the reverse Warburg effect[17,18], metabolic symbiosis[19,20], and addiction to glutamine metabolism[21,22], create challenges for anti-cancer treatment due to adaptive or acquired chemoresistance. This review article focuses on the relationship between metabolic reprogramming and tumor heterogeneity, as well as on the development of promising therapeutic strategies by drug repositioning targeting metabolic reprogramming.

Cancer and Its Classification

Cancer is a general term applied of series of malignant diseases that may affect different parts of Body. These diseases are characterized by a rapid and uncontrolled formation of abnormal cells, Which may mass Together to form a growth or tumor, or proliferate throughout the

body, initiating Abnormal growth at other sites. If the process is not arrested, it may progress until it causes the Death of the organism. The main forms of Treatment for advance stage cancer in humans are surgery, Radiation and drugs (cancer chemotherapeutic Agents)

Types of Cancer

1. Cancer of Blood and Lymphatic Systems

a)Hodgkin's disease, b) Leukemia's, c)Lymphomas, d) Multiple myeloma, e) Waldenstrom's disease

2. Skin Cancers

a). Malignant Melanoma

3 Cancers of Digestive Systems

a). Esophageal cancer b) Stomach cancer c) Cancer of pancreas d) Liver cancer

e) Colon and Rectal Cancer f) Anal cancer

4. Cancers of Urinary system

a).Kidney cancer b) Bladder cancer c) Testis cancer d) Prostate cancer

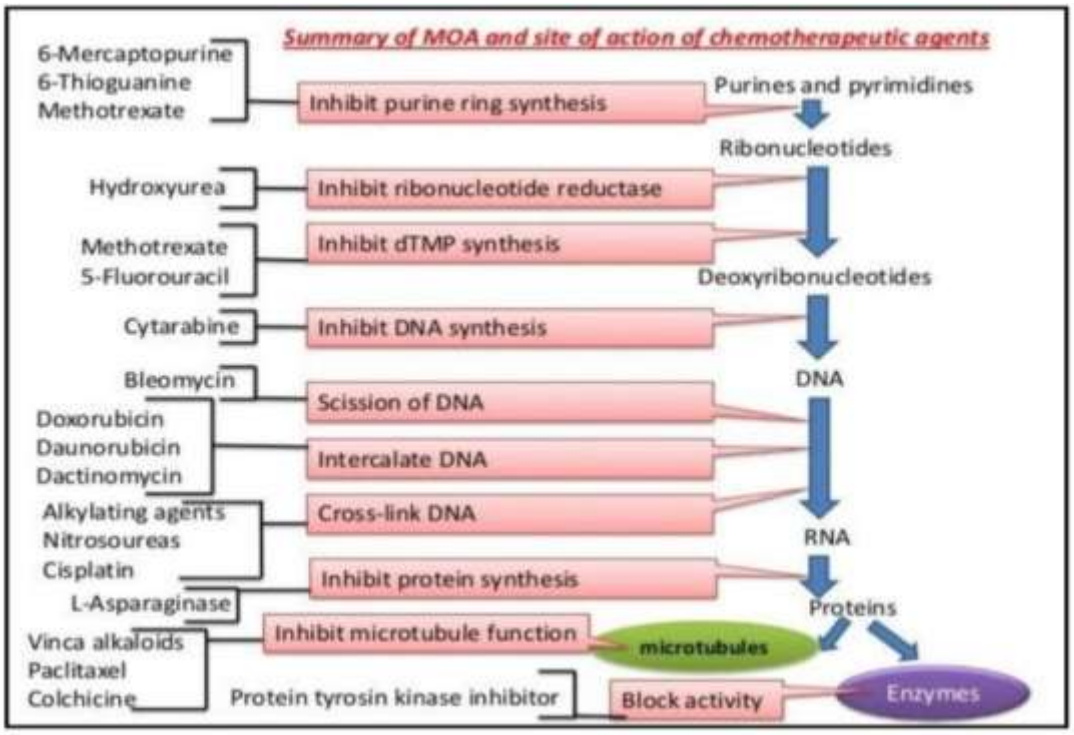
5. Cancers in women

a).Breast cancer b) Ovarian cancer c) Gynecological cancer d) Choriocarcinoma

6. Miscellaneous cancers

A). Brain cancer b) Bone cancer c) Characinoid cancer d) Nasopharyngeal cancer e) Retroperitoneal Sarcomas f) Soft tissue cancer g) Thyroid cancer

The Mechanism on Cancer Therapy



Conventional Warburg effect and emerging concepts

In 1924, Otto Warburg discovered that tumor cells tend to produce large amounts of lactate from glucose, regardless of the available oxygen level.[15,16] This situation is similar to anaerobic glycolysis, implying that oxidative phosphorylation (OXPHOS) is replaced by glycolysis in normal differentiated cells under hypoxia.[23, 24] However, cancer cells appear to engage in glycolytic metabolism before they are exposed to hypoxic conditions.[15,16] OXPHOS in mitochondria generates as many as 36 mol ATP from 1 mol glucose, whereas the conversion of glucose to pyruvate or lactate produces only 2 or 4 mol ATP, respectively.[25, 26] It remains unclear why cancer cells largely depend on this "inefficient" metabolic pathway, even when enough oxygen is available.[27, 28] In striking contrast to normal cells, cancer cells preferentially uptake and convert glucose into lactate even in the presence of sufficient oxygen.[29] This seemingly "inefficient" metabolic characteristic relies largely on aberrant upregulation of GLUT1, a glucose transporters abundantly expressed in cancer cells[30, 31], although one contradictory study reported that GLUT1 is not necessarily involved in the Warburg effect depending on the degree of tumor invasiveness.[32] Inefficient ATP synthesis becomes an obstacle for cancer cells only when their energy resources are scarce. However, this is not the case in proliferating cancer cells with aberrant angiogenesis.[29] Tumor cells finely regulate ATP synthesis by regulating substrate uptake, as well as enzymes related to

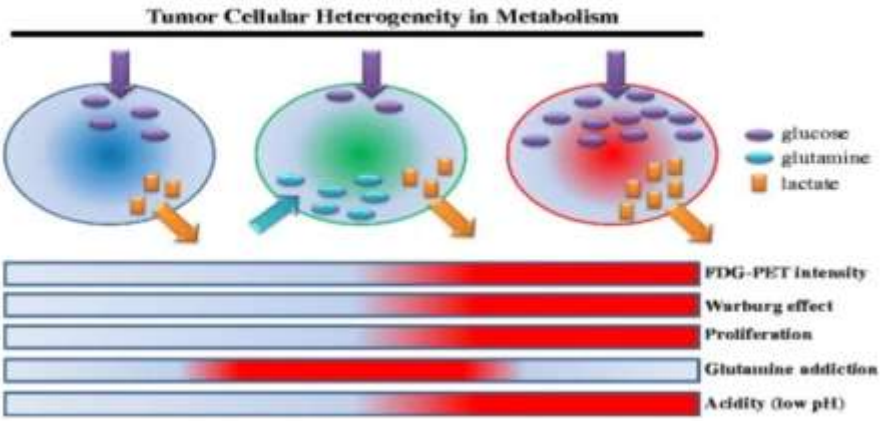
glycolysis, which enables them adapt to the nutrient microenvironment.[33] Moreover, the regulation of adenosine monophosphate-activated protein kinase (AMPK) signal transduction, a sensor of energy status, is intimately connected to the Warburg effect, one form of metabolic reprogramming of cancer cells.[34, 35]

Indeed, genetic ablation of AMPK activates mammalian target of rapamycin (mTOR) signal with ectopic expression of hypoxia-inducible factor-1 alpha (HIF-1 alpha), resulting in rapid cellular proliferation accompanied by activation of aerobic glycolysis.[35] This strongly suggests the importance of cancer metabolic reprogramming in maintaining the interaction between the oxygen-sensing transcription factor and the nutrient-sensing signal pathway.

Metabolic reprogramming in response to chemotherapy

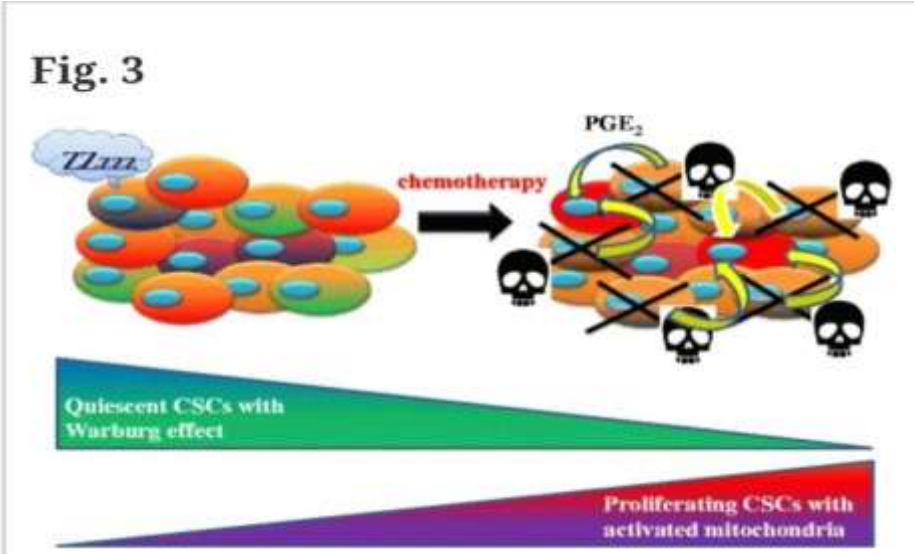
Tumor heterogeneity in regard to mitochondrial metabolism, in seeming contradiction to the Warburg effect, is considered to induce the diversity in activated metabolic pathways[36] (Fig. 2). Notably, MRD in several kinds of cancers is enriched in CSCs, leading to intra-tumoral heterogeneity and poor prognosis.[1, 9, 10, 37] Non-CSCs of bladder cancer, for instance, release prostaglandin E2 (PGE2) when they undergo apoptosis during the course of chemotherapy. PGE2 promotes the awakening of dormant G0-phased CSCs into the proliferative state.[9] Given that PGE2-mediated metabolic activation in mitochondria has been demonstrated in non-malignant cells[38], it is possible that activated CSCs undergo altered metabolic reprogramming (Fig. 3). Similarly, the survivors after transient depletion of a driver oncogene (i.e., activated mutant KRAS G12D in pancreatic cancer) tend to depend heavily on OXPHOS in mitochondria rather than aerobic glycolysis. Comprehensive analysis of metabolic pathways of survivors after chemotherapy revealed the prominent expression of genes that regulate mitochondrial function, autophagy and lysosome degradation activity, as well as a strong reliance on mitochondrial respiration and diminished dependence on the Warburg effect.[10] Autophagy is a metabolic-recycling pathway involving proteasomeindependent degradation of cellular components (e.g., old and dysfunctional mitochondria), which is partially responsible for cancer chemoresistance.[39]

Fig. 2



Tumor heterogeneity in metabolism. The degree of addiction to glucose or glutamate differs among various types of cancer cells. Tumor cells robustly importing glucose via the GLUT1 transporter are responsible for the high intensity of FDG-PET in the clinical settings. Cancer cells that express high levels of GLUT1 also induce a low-pH acidic tumor microenvironment, thereby increasing the invasive potential of tumors.

Fig. 3



Iatrogenic activation of CSCs with altered metabolic reprogramming. Non-CSCs are susceptible to chemotherapy and undergo apoptosis. Released PGE2 awakens the dormant CSCs localized in the niche. Proliferating CSCs are likely to exhibit additional metabolic reprogramming, concomitant with upregulation of OXPHOS-related molecules.

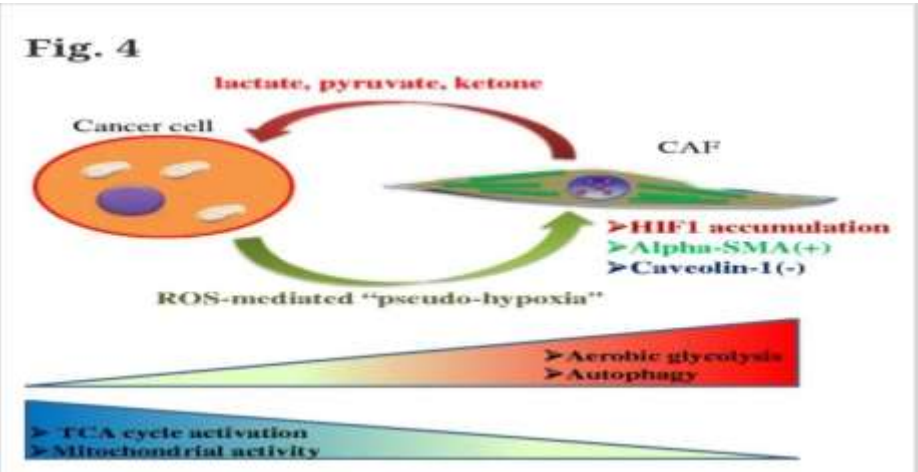
Furthermore, malignant melanoma cells that survive and proliferate after treatment with mutant BRAF (V600E) inhibitor tend to exhibit relative dependence on mitochondrial

metabolism.[11] Because BRAF suppresses oxidative phosphorylation (OXPHOS), MRD cells up-regulate proliferator-activated receptorgamma coactivator-1 (PGC1-alpha). The BRAF (V600E)-MITF-PGC1-alpha axis promotes the biogenesis of mitochondria and causes BRAF-mutant melanoma cells to become addicted to mitochondrial metabolism.[11] Because histone H3 lysine 4 (H3K4)-demethylase JARID1B-highly expressing melanoma cells proliferate slowly and are highly dependent on mitochondrial metabolism[11,40], chemotherapyinduced metabolic reprogramming in tumor tissue is likely to be responsible for the enrichment of CSCs in MRD.

Metabolic interaction driven by tumor heterogeneity

Initially, the concept of Warburg effect was believed to be confined to cancer cells. More recently, the emerging concept of the "reverse Warburg effect", however, has attracted considerable attention. Tumor cell-derived reactive oxygen species (ROS) decrease the expression of caveolin-1 in cancer-associated fibroblasts (CAFs). CAFs are the major component of tumor stroma, and as such they express alphasmooth muscle actin (alpha-SMA) and are widely recognized to drive tumor progression and metastasis.[41] Loss of caveolin-1 in CAFs results in elevated ROS levels, which in turn stabilize HIF-1 alpha.[17, 42]

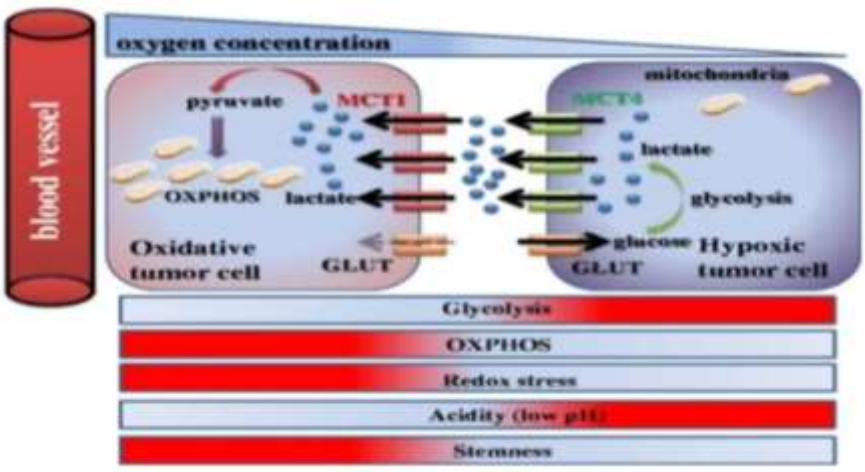
In brief, cancer cells create "pseudo-hypoxic" conditions for fibroblasts. Because the transcription factor HIF-1 alpha promotes glycolysis and provides tumor cells with lactate and glutamate, elevated production of ROS in cancer cells indirectly induces uptake of intermediate metabolites of the tricarboxylic acid (TCA) cycle in mitochondria. CAFs consume more glucose and secrete more lactate than normal fibroblasts. Furthermore, CAFs depend significantly on autophagy, and the activation of autophagy in tumor stroma leads to chemoresistance[18, 42] (Fig. 4).



Interaction of caveolin 1-deficient CAFs with tumor cells. Cancer cells induce a pseudo-hypoxic microenvironment rich in ROS derived from metabolic reprogramming. By contrast, CAFs negative for caveolin 1 provide tumor cells with lactate, pyruvate, and ketone bodies. Notably, although cancer cells depend heavily on mitochondrial metabolism, CAFs exhibit the Warburg effect and activation of the autophagic pathway.

As mentioned above, fibroblasts surrounding epithelial cancer cells undergo metabolic reprogramming resembling the phenotype associated with the Warburg effect. Metabolic symbiosis between epithelial cancer cells and CAFs requires that each cell express a different subtype of monocarboxylate transporter (MCT). Epithelial cancer cells express MCT1, which contributes to uptake of lactate provided by caveolin1-null CAFs expressing MCT4.[17, 43] Tumor cells synthesize pyruvate from lactate, providing the TCA cycle with an intermediate metabolite. Notably, an extracellular space rich in lactate reflects acidic conditions, which in turn lead to the formation of pseudo-hypoxic conditions.

It should be emphasized, however, that this reverse Warburg effect is not necessarily present in all tumor types. Tumors expressing high levels of MCT4 or mesenchymal phenotype do not tend to exhibit the reverse Warburg phenomenon. Instead, cancer cells exhibit hierarchical metabolic heterogeneity: MCT4expressing tumor cells perform glycolysis and secrete lactate via MCT4, whereas MCT1-expressing cells import lactate via MCT1 and perform OXPHOS. In addition, the amount of glucose uptake is lower in MCT1-positive cancer cells than in MCT4-positive cells[19, 20] (Fig. 5). This metabolic heterogeneity is referred to as metabolic symbiosis, and this kind of lactate shuttle is also observed between neurons and astrocytes in the normal brain tissue.[44] It is notable that normal and cancerous tissues share finely regulated mechanisms of metabolic symbiosis.



Metabolic symbiosis between oxidative/aerobic tumor cells and hypoxic/glycolytic cells. Tumor heterogeneity induces a lactate shuttle between hypoxic and oxidative cancer cells. While MCT4-positive hypoxic cells contribute to formation of an acidic microenvironment by aerobic glycolysis and secretion of lactate, MCT1-expressing oxidative cells utilize lactate as a substrate of the TCA cycle, and consequently exhibit stem-like characteristics. Notably, in contrast with MCT1-positive cancer cells, glucose uptake is robust in MCT4-expressing cells.

Cancer stem-like cells in metabolic symbiosis

Importantly, well-oxygenated/aerobic cancer cells expressing high levels of MCT1 efficiently produce metabolic intermediates, as well as ATP, by utilizing lactate derived from hypoxic/glycolytic cells expressing high levels of MCT4. Redox stress is a major hallmark of cancer tissues that drives robust metabolism in adjacent proliferating MCT1-positive cancer cells, which are rich in mitochondria, mediated by the paracrine transfer of mitochondrial fuels such as lactate, pyruvate, and ketone bodies[19,20] (Figs. 4 and 5).

Most importantly, genotoxic stress due to chemotherapy or irradiation, which increase ROS levels, promotes a CSC-like phenotype.[45–47] Because CSCs exhibit a rapidly proliferating and poorly differentiated phenotype, MCT1-positive cancer cells are likely to harbor stem-like phenotypes in heterogeneous populations of tumor cells. After all, activated mitochondrial metabolism produces enough energy not only for self-renewal by proliferation but also for invasion/distant metastasis, both of which are activated in CSCs.

Thus, the pharmacological blockage of MCT1 is useful for the treatment of cancer. MCT1 inhibition disrupts metabolic symbiosis, and MCT1-positive aerobic cancer cells can no longer uptake lactate[20], which suggests that MCT1-positive CSCs play a fundamental role in maintaining the hierarchy in tumor cellular society, in contrast to MCT4-positive cells (Fig. 5).

Acquisition of stem-like and malignant phenotypes with metabolic reprogramming

The cooperation of amino acid transporters is necessary for cancer cells to undergo metabolic reprogramming and maintain stem-like phenotypes. For example, triple-negative breast cancer (TNBC) cells, which lack estrogen receptor, progesterone receptor, and the tyrosine kinase receptor HER2, exhibit addiction to glutamine metabolism due to coordination between the xCT and ASCT2 amino acid transporters[48,49]: xCT uptakes cystine in exchange

for glutamine, for use in GSH synthesis[7], whereas ASCT2 uptakes glutamine in a collaborative manner.[50] Glutamine is simultaneously imported via ASCT2 transporter and exported in exchange for leucine via the LAT1/4F2 (CD98 heavy chain) antiporter.[48] The glutamine uptake pathway contributes to the synthesis of alpha-KG, promoting the TCA cycle in mitochondria, as well as glutamate, thereby promoting synthesis of nucleotides required for cellular proliferation[48] (Fig. 6). Thus, metabolic reprogramming, which is orchestrated by the elevated expression and interaction of amino acid transporters, contributes to the activation of glutamine metabolic reprogramming and protects tumor cells against accumulation of oxidative stress mediated by cystine metabolic reprogramming.

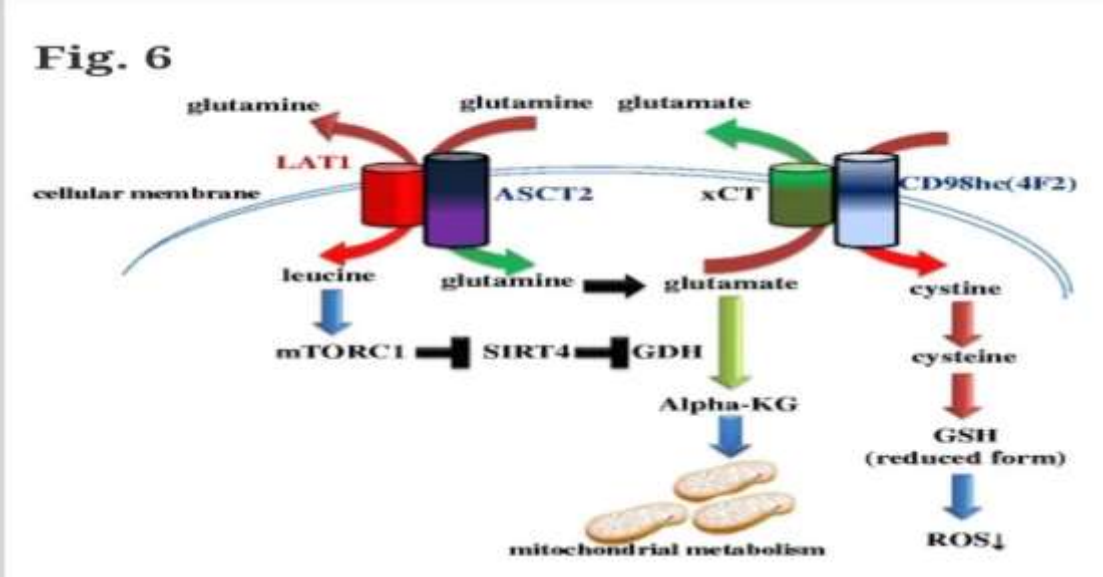


Fig. 6

Metabolic reprogramming of amino acids due to coordinated transporters. ASCT2/LAT1 and xCT/CD98hc transporter complexes in tumor cells activate the mTORC1-SIRT4-GDH axis and glutathione synthesis, respectively. The former pathway promotes conversion of glutamate into alpha-KG, a substrate of the TCA cycle, whereas the latter pathway maintains redox status.

Remarkably, circulating tumor cells (CTCs) that have undergone metabolic reprogramming provide themselves with a microenvironment that is favorable for colonization and distant metastasis. Recent work showed that CTCs derived from colon adenocarcinoma and positive for CD110, the thrombopoietin receptor, can home to the pre-metastatic niche and colonize metastatic hepatic tissue due to elevated lysine catabolism.[51, 52] Lysine degradation provides CD110-positive CTCs with glutamate and acetylCoA, which contributes to the synthesis of

anti-oxidant GSH and p300-dependent LRP6 acetylation, respectively.[52, 53] This metabolic reprogramming promotes the metastatic potential of CTCs via a reduction in ROS levels, elevation of self-renewal potential, and activation of the Wnt/beta-catenin signal pathway.[52] Thus, CTCs resemble CSCs during the process of metastasis, at least in terms of the 'education' of the pre-metastatic niche. Most importantly, this metastatic phenotype is supported by lysine metabolic reprogramming.

A subpopulation of cancer cells that depend heavily on aerobic glycolysis robustly uptakes and consumes glucose, whereas another subpopulation engages in OXPHOS and glutaminolysis with activated mitochondrial metabolism. The efficiency of lactate production in the former (MCT4-positive) subpopulation is much higher than in the latter (MCT1-positive) subpopulation, which relies on OXPHOS and glutamine-derived TCA cycle in the mitochondria[54] (Fig. 5). Thus, tumor cells tend to decrease microenvironmental pH via elevated lactate secretion. The acidic tumor microenvironment induces expression of matrix metalloproteinases (MMPs), especially MMP-2 and MMP-9.[55] Thus, metabolic reprogramming remarkably enhances the invasion and metastatic potentials of cancer cells.

Activation of glutamine metabolism driven by oncogene addiction Mitochondria plays a much more important role in cancer metabolism than previously expected, and glutaminolysis is the most common metabolic pathway regulated in this organelle.[56] Glutaminolysis is the series of biochemical reactions by which glutamine is catabolized into downstream metabolites, e.g., alpha-ketoglutarate (alpha-KG) and glutamate. Via the TCA cycle, alpha-KG undergoes catabolism to malate, which is transported into the cytoplasm and converted to pyruvate, and then ultimately to lactate.[22] Mechanistically, mTORC1 signaling promotes glutamine anaplerosis via upregulation of glutamate dehydrogenase (GDH).[57] SIRT4 is a mitochondrial-localized member of the sirtuin family of NAD-dependent enzymes that play fundamental roles in metabolism, stress response and longevity.[58] In regard to glutaminolysis, SIRT4 is a critical negative regulator for glutamine metabolism in mitochondria[58], which is down-regulated at the transcriptional level when the mTOR signaling pathway is activated.[57] Thus, mTOR inhibitors such as rapamycin are expected to block mTORC1-SIRT4-GDH axis, which is essential for glutaminolysis.[57]
(Fig. 6).

As mentioned above, tumor tissue consists of a cellular population that is heterogeneous in terms of dependency on the Warburg effect and mitochondrial metabolism. Relative to slow-

cycling CSCs, proliferative cancer cells tend to take up a great deal of glutamine, as well as glucose, for the generation of metabolites.[54] Both aerobic glycolysis and glutaminolysis are frequently simultaneously activated in malignant cancer cells.[36,59] Seemingly paradoxically, however, some cancer cell lines cannot survive and proliferate in the absence of glutamine, despite the fact that glutamine is a non-essential amino acids that can be synthesized from glucose.[60] Glutamine is a primary substrate for the TCA cycle and is required to maintain the redox state via the production of nicotinamide adenine dinucleotide phosphate (NADPH). Glutaminolysis enables cancer cells to reduce NADP+ to NADPH, a reaction that is catalyzed by malic enzymes. NADPH is a required electron donor for reductive steps in lipid synthesis, nucleotide metabolism, and maintenance of reduced GSH.[21] In this way, metabolic reprogramming of glutaminolysis enables cancer cells to regulate redox state.

Oncogenic c-Myc mediates elevation of glutaminolysis in cancer cells. C-Myc promotes both glutamine uptake and glutamine catabolism.[61] Because of c-Myc-mediated metabolic reprogramming, cancer cells tend to exhibit “glutamine addiction”.[48,61] This is a typical example of metabolic reprogramming in cancer cells with oncogene-addiction[62,63], suggesting a potential “Achilles’ heel” of tumor cells that are addicted to glutamine metabolism in manner that is mediated by c-Myc.

CONCLUSIONS

The complex and dynamic metabolic reprogramming should be regarded as a reflection of the “robustness” of tumor cells against unfavorable conditions. Hyper-adaptation due to metabolic reprogramming of cancer cells is likely to give us a great opportunity to attack the “shatter point” in heterogeneous tumor tissue. DR enables us to identify “silver bullets” for the treatment of tumor tissues in metabolically heterogeneous cell populations. To facilitate development of novel therapeutic strategies, the synergistic effects of repositioned drugs with conventional anti-cancer agents should be evaluated in clinical trials in the near Medicinal plants maintain the health and vitality of individual and also cure various diseases Including Cancer without causing toxicity. Natural products discovered from medicinal plants have Played an important Role in treatment of cancer. In this review some anti cancer plants have been Presented. These plants possess Good immunomodulatry and antioxidant properties leading to Anticancer activity. In conclusion this article Provides the knowledge about anticancer medicinal Plants of foreign origin, which are used by people all over The world. Also it is of sigsnificance to Exploit novel anticancer drugs from medicinal plants. Without

this early Warning system, the Problem of overcoming development of chemoresistance is quite considerable. In an ideal Situation, Therapy would be tailored to suit the individual at the outset; this is unlikely at least for the very near Future, despite rapid progress in pharmacogenomics. In the meantime, a better understanding of the Mechanisms Of resistance will at least allow the physician to modulate the therapy on a need to do Basis. Medicinal plants Have contributed a rich health to human beings. Plant extracts and their Bioactive compounds present in them Which are responsible for anticancer activity have to be Screened for their valuable information. This review had Given some of the plants possessing Anticancer activity for various types of cancer.

Abbreviations

Alpha-KG: Alpha- ketoglutarate

AMPK: Adenosine monophosphate-activated protein kinase

CAFs: Cancer-associated fibroblasts

CSC: Cancer stem-like cell

CTC: Circulating tumor cells

DM: Diabetes mellitus

DR :Drug-repositioning

ECM: Extracellular matrix

ENPP1: Ectonucleotide pyrophosphatase/phosphodiesterase family member 1

GDH: Glutamate dehydrogenase

HIF-1 alpha: Hypoxic inducible factor-1 alpha

LAT1: L-type amino acid transporter 1

MCT: Monocarboxylate transporter

MMP: Matrix metalloproteinases MRD: Minimal residual disease mTOR: Mammalian target of rapamycin

NADPH: Nicotinamide adenine dinucleotide phosphate

OXPHOS: Oxidative phosphorylation

ROS: Reactive oxygen species

TCA: Tricarboxylic acid

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