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An update on therapeutic opportunities offered by cancer glycolytic metabolism

Carlotta Granchi [a], Daniele Fancelli [b], Filippo Minutolo [a,*]

[a] Dipartimento di Farmacia, Università di Pisa, Via Bonanno 6, 56126 Pisa, Italy
[b] Drug Discovery Program, Experimental Oncology Department, European Institute of Oncology IEO, Via Adamello 16, 20139 Milan, Italy

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ABSTRACT

Almost all invasive cancers, regardless of tissue origin, are characterized by specific modifications of their cellular energy metabolism. In fact, a strong predominance of aerobic glycolysis over oxidative phosphorylation (Warburg effect) is usually associated with aggressive tumour phenotypes. This metabolic shift offers a survival advantage to cancer cells, since they may continue to produce energy and anabolites even when they are exposed to either transient or permanent hypoxic conditions. Moreover, it ensures a high production rate of glycolysis intermediates, useful as building blocks for fast cell proliferation of cancer cells. This peculiar metabolic profile may constitute an ideal target for therapeutic interventions that selectively hit cancer cells with minimal residual systemic toxicity. In this review we provide an update about some of the most recent advances in the discovery of new bioactive molecules that are able to interfere with cancer glycolysis.

Deregulation of cellular energetics is emerging as one of the most important hallmarks of cancer.[1] Among the many adjustments of the metabolic pathways that are found in tumor cells, a key role is played by an enhanced aerobic glycolysis followed by lactic fermentation, which is also known as the Warburg effect.[2] In fact, normal cells generally transform glucose into carbonic anhydride under aerobic conditions, by means of oxidative phosphorylation (OXPHOS). On the contrary, invasive cancer cells mostly produce lactate, even in the presence of sufficient levels of oxygen, although this glycolytic pathway turns out to be less efficient than OXPHOS in producing ATP units. This apparently counterproductive behavior of cancer cells actually constitutes a survival advantage in rapidly proliferating cells, since it make them insensitive to transient or permanent hypoxic conditions, it contributes to the production of nucleosides and aminoacids, and, thanks to the enhanced glucose uptake occurring in cancer tissues, constitutes a very rapid way to produce energy. Furthermore, lactate is not just a waste product of this process; on the contrary, it promotes tumor invasion by favoring cell migration, angiogenesis, immune escape and radioresistance.[3] This redirection of glucose metabolism is promoted by the overexpression of the many effectors of the glycolytic pathway, consisting of specific membrane transporters of glucose (GLUTs) and lactate (MCTs), as well as of all the enzymes responsible for the promotion of each single step of the cascade involved in the transformation of glucose into lactic acid. This type of modifications raised questions about the possibility that cancer is a metabolic disease, which may be actually initiated by an impairment of some of the mitochondrial functions.[4] Regardless its origin, the metabolic shift present in most invasive cancer tissues may lead to the development of new means to selectively counteract cancer progression, without causing significant damages to healthy cells.[5] Several reviews dealing with compounds that target cancer metabolism have been published in the near past.[6–9] We herein provide an update of the most significant recent advances in the development of 'antiglycolytic' anticancer agents, which have been classified on the basis of their principal targets.

Glucose transporters (GLUTs): Glucose transporters (GLUTs) constitute a family of proteins that regulate the transport of glucose across the hydrophobic cell membranes. As of today 14 isoforms of the GLUT genes have been identified, which show similar structural architecture but different cellular and sub-cellular localization, kinetic properties and affinity for glucose and other hexoses. Different GLUTs have been found to be overexpressed in a wide variety of cancer types, and their level of expression often correlates with the metastatic potential and worse prognosis of the tumor.[10] In particular, over the past few years GLUT1 has been regarded as a potential target in oncology drug discovery. Very recently, a human GLUT1 crystal structure was obtained, and this achievement will surely be helpful in the discovery of new GLUT1 inhibitors as anti-cancer agents.[11]

* Corresponding author. Tel.: +39 050 2219 557; fax: +39 050 2219 605.
E-mail address: filippo.minutolo@farm.unipi.it (F. Minutolo).

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A series of polyphenolic esters were found to inhibit glucose transport through the cell membrane, and to exert a certain antiproliferative activity in the H1299 lung cancer cell line.[12,13] The initial development of this class led to WZB117 **1** (Fig. 1), which showed 93% inhibition in a standard glucose uptake assay and 41% inhibition of cancer cell growth rate (IC_{50} = 10 μM in cell viability assays) in lung cancer cells, with a more pronounced antiproliferative effect under hypoxic conditions. Compound **1** proved to exert its antiproliferative activity selectively on tumor cells, as demonstrated by growth inhibition in lung (A549) and breast (MCF7) cancer cells lines, without being effective on their corresponding non-tumorigenic counterparts (NL20 and MCF12A, respectively). In an A549 xenograft model of human lung cancer WZB117, dosed intraperitoneally daily at 10 mg/kg, induced more than 70% reduction of tumor volume without any significant side effects, with the exception of a mild and reversible hyperglycemia. Further studies using human red blood cells, which uniquely express GLUT1 as the glucose transporter, confirmed that WZB117 specifically targets GLUT1 isoform in the inhibition of glucose transport. Co-administration of WZB117 with the mitochondrial inhibitor oligomycin led to a synergistic reduction of proliferation of A549 lung cancer cells. At a dose (50 nmol/L) at which oligomicin alone does not exert significant antiproliferative effect, co-administration with WZB117 sensitizes cancer cells to GLUT inhibition and induces cell cycle arrest, senescence and, finally, necrosis.[14]

Natural compound (+)-cryptocaryone **2** (Fig. 1) has been recently identified among the components of an extract isolated from the leaves and twigs of *Cryptocarya rubra*, a tropical plant belonging to the Lauraceae family.[15] This extract was found to be cytotoxic on HT-29 human colon cancer cells, as widely reported in the literature, where there are many evidences of the cytotoxicity of this dihydrochalcone on cancer cell lines, such as its ability to induce apoptosis through activation of caspases in prostate tumor.[16,17] Consistent with previous data, compound **2** showed an IC_{50} value of 0.32 μM on HT-29 cells, and was found to cause a significant reduction of the uptake of glucose, implying that its anti-proliferative activity could be ascribed, at least in part, to GLUT inhibition.

Some members of a class of oxime derivatives, which had been previously designed as estrogen receptor (ER) ligands[18] revealed to be active as GLUT1-inhibitors. These compounds show some common pharmacophoric similarities with WZB117-like inhibitors, mainly consisting in the presence of similarly-spaced peripheral 'phenol-type' OH groups.[19] Aldoximes **3** and **4** (Fig. 1), which differ only for a fluorine atom in *meta* position of the distal phenyl ring, displayed IC_{50} values of 8.5 μM (**3**) and 23.4 μM (**4**) in the glucose uptake assay, whereas ketoximes **5** and **6** (Fig. 1), which, similarly

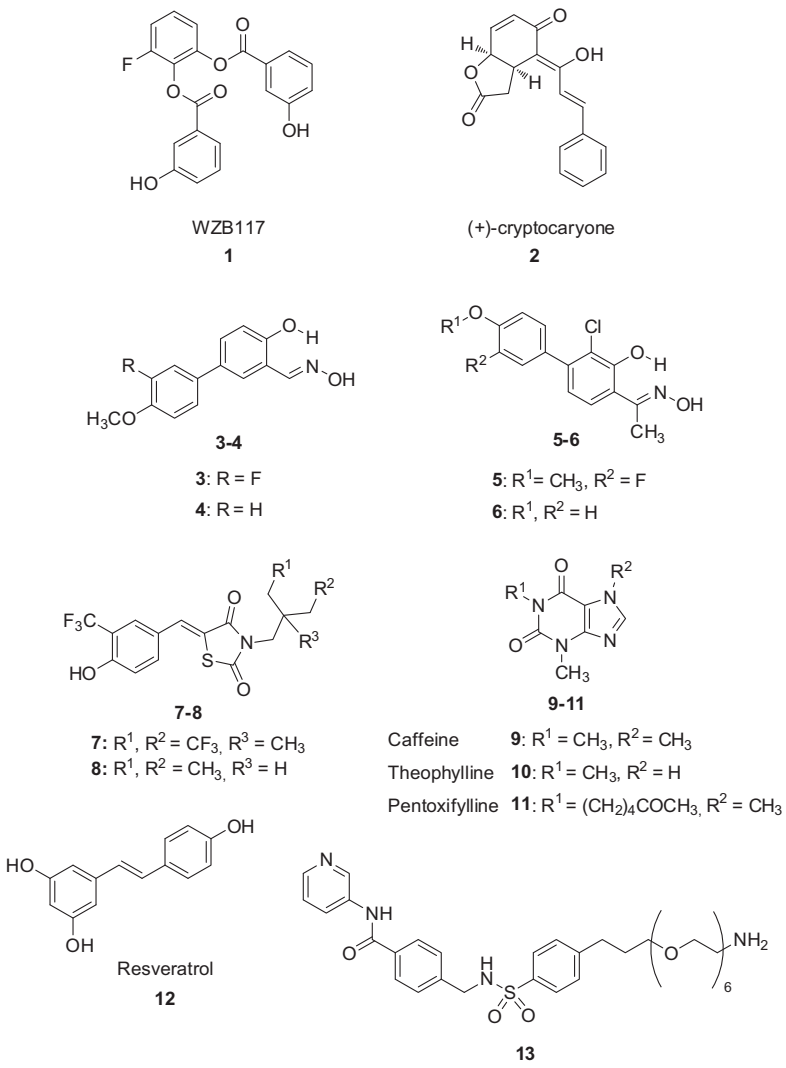

Figure 1. Structures of GLUT inhibitors.