Dichloroacetate is an antimetabolite that antagonizes acetate and deprives cancer cells from its benefits: A novel evidence-based medical hypothesis


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ABSTRACT

Dichloroacetate (DCA) is a promising safe anticancer drug that cured a patient with chemoresistant non-Hodgkin’s lymphoma and treated lactic acidosis effectively. The well-known mechanism of DCA action is through stimulating Krebs cycle (stimulating pyruvate dehydrogenase via inhibiting pyruvate dehydrogenase kinase). This prevents lactate formation (Warburg effect) depriving cancer cells of lactate-based benefits e.g. angiogenesis, chemoresistance and radioresistance. Here, we introduce novel evidence-based hypotheses to explain DCA-induced anticancer effects. On pharmacological and biochemical bases, we hypothesize that DCA is a structural antagonist of acetate competing with it for target enzymes and biological reactions. We hypothesize that DCA exerts its anticancer effects via depriving cancer of acetate benefits. We hypothesize also that acetate is an antidote of DCA capable of treating DCA toxicity. Many reports support our hypotheses. Acetate is vital for cancer cells metabolism and survival as elevated acetate can drive resistance to targeted cancer treatments. Acetate is required for epidermal growth factor receptor vIII mutation in lethal brain tumors. Experimentally, DCA inhibited acetate oxidation in hearts of normal rats and reversed inhibitory effects of acetate on the oxidation of glucose. During presence of DCA with no glucose in heart perfusions with [1-14C]acetate, DCA decreased the specific radioactivity of acetyl CoA and its product citrate. This proves our hypotheses that DCA is an antimetabolite that antagonizes acetate for vital reactions in cancer cells. Acetate may be used as an antidote to combat DCA toxicity.

Introduction

Monochloroacetate (MCA), dichloroacetate (DCA), and trichloroacetate (TCA) are chlorinated acetates that are formed during water disinfection processes [1]. DCA results in daily life from water chlorination [2] and is also a promising drug treatment for treating mitochondrial diseases, pulmonary arterial hypertension and cancer [3]. In clinical oncology, DCA emerged as a promising safe anti-neoplastic agent causing cancer cells apoptosis via targeting the enzyme pyruvate dehydrogenase kinase (PDK) that regulates initiation of Krebs cycle using pyruvate [4]. Depriving cancer cells of lactate is vital as a cancer therapeutic strategy due to the numerous lactate-based benefits.
DCA. Acetate caused a decrease in serum potassium, phosphorus and glucose, and an increase in serum lactate, citrate, free fatty acids and ketone bodies (serum acetocetate and beta-hydroxybutyrate levels). Acetate decreased the proportion of active (dephosphorylated) pyruvate dehydrogenase in perfused rat heart. DCA produced quite opposite effects [12]. Regarding the effects of intravenous acetate infusion on pH, acetate produced metabolic alkalalemia while DCA infusion caused minimal effects on acid-base state and oxygen consumption [12]. All these evidences prove that DCA is a competitive antagonist of acetate.

There are many reports that support our idea that DCA works through antagonizing acetic acid (Table 2). DCA inhibited extraction of plasma free fatty acids (as acetic acid) in heart tissues from normally fed rats and also from alloxan-induced diabetic rats. In heart perfusions with glucose, insulin and acetate (stimulators of glycolysis and subsequently Krebs cycle), DCA decreased the cell citrate concentration (product of Krebs cycle). DCA was also reported not to be metabolized to dichloroacetyl-CoA, dichloroacetylcarnitine, citrate or CO$_2$ [13], which supports the hypothesis that DCA acts as an antagonist that inhibits the enzyme activity without being metabolized. This supports also that DCA is an enzyme inhibitor that does not undergo further metabolism. In the absence of glucose and insulin (stimulators of glycolysis and subsequently Krebs cycle), DCA inhibited glycolysis as a source of acetyl CoA causing no increase in acetyl CoA levels [13]. Taking into account that acetate is vital for many tumor types, its possible antagonism by DCA can be a novel mechanism for DCA-induced cancer cell cytotoxicity.

The vital question that arises now: is acetate itself important for cancer cells metabolism and survival?

**Acetate promotes tumor growth**

Acetate is a bioenergetic substrate for human glioblastoma and brain metastases. Elevated acetate levels can drive resistance to targeted cancer treatments. Treatment with sequentially increasing concentrations of acetic acid was reported to persistently enhance RNA, protein, and DNA synthesis. That was followed by extensive epidermal hyperplasia [14]. Based on that, acetate promotes synthesis of DNA and macromolecules essential for cancer cell division. Either glucose or acetate is required for the activation of epidermal growth factor receptor vIII (a common growth factor receptor mutation in the fatal brain cancer glioblastoma multiforme). Moreover, elevated energetic nutrient levels (acetate or glucose) can induce resistance to targeted cancer treatments [15]. Also, acetate is an epigenetic regulator of posttranslational protein modification, and is a carbon source for cancer cell biomass accumulation. Acetate plays a major role in protein acetylation and acetate oxidation plays an important role in carcinogenesis, cancer progression and treatment [11].
growth of tumors. This was confirmed by positron emission tomo-
graphy (PET) imaging studies using [11C]acetate where many tumor
types are dependent on acetate as a source of carbon to get acetyl-CoA.
Excessive acetate uptake was reported in prostate, lung, liver, and brain
cancers [16–19]. Tumors exhibit acetate dependence. Acetate con-
stitutes a vital supply of acetyl-CoA for feeding these tumors [20]. Inter-
estingly, [11C]acetate PET imaging is preferred than [18F]fluor-
odeoxyglucose (FDG) PET imaging as [11C]acetate PET imaging is
more accurate and sensitive. Acetate consumption by human tumors is
evident by nuclear magnetic resonance (NMR). Acetyl coA synthase
seems to be of paramount importance to consume acetate as a supply of
acetyl-CoA. Primary and metastatic mouse orthotopic brain tumors
have the capacity to oxidize acetate and glucose. Acetate consumption
in such tumors correlated with the expression of acetyl-CoA synthetase
enzyme [21].

Consequences of the hypothesis and discussion

DCA exerts potent promising anticancer effects. DCA exerted anti-
proliferative and pro-apoptotic effects against many cancer cells. DCA
was reported to reverse the glycolytic phenotype and inhibit metastasis
of breast cancer cells both in vitro and in vivo [22]. DCA treatment
was reported to reduce cancer cell-induced production of lactate and to
sensitize malignant cells to 5-fluorouracil in gastric cancer cells [23].
Moreover, DCA reduced cancer cells (hypoxic HeLa cells) proliferation,
viability and colony counts [24]. Unlike many chemotherapeutics, hy-
poxia (a common criterion of cancer biology) enhances the antitumor
activity of DCA [25].

Interestingly, DCA killed cancer stem cells effectively e.g. embry-
onal carcinoma stem cells (shares in teratocarcinoma development that
exhibited strong dependence on glycolysis with decreased mitochon-
drial biogenesis) [26]. Till now, DCA-induced anticancer effects are
looked at as through stimulating Krebs cycle via inhibiting PDK
causing stimulation of pyruvate dehydrogenase complex where acetyl
CoA starts Krebs cycle through combination with oxaloacetate to form
citrate. This necessitates that glycolysis reaction becomes aerobic and
not anaerobic (ending in formation of lactate, Warburg effect). Tumor
glycolysis-induced pyruvate is converted into lactate (Warburg effect
that confers many lactate-based benefits to cancer cells e.g. angiogen-
esis, chemoresistance and radioresistance [5]. Based on that, DCA
clearly reverses cancer glycolytic phenotype and exerts potent antic-
ancer effects.

Future perspectives based on our evidence-based hypothesis include
many points. Our hypotheses will guide scientific research in this di-
rection to open a new research frontier towards many investigations
based on our hypothesized points that DCA antagonizes acetate.
The following practical research points and applications may benefit med-
ical practice:

1. An experimental design to investigate acetate-induced inhibition of
DCA-induced cell death.
2. An experimental biochemical design to investigate the enzyme ki-
netics of DCA-induced antagonistic effects of acetate and the effects of
DCA on acetate-based enzyme systems e.g. acetyl CoA synthase
enzyme [27].
3. Future possibility of using acetic acid-based treatments as antitoxins
and antagonists of DCA to combat DCA accidental toxicity and
poisoning.
4. Acetate dependence of tumors can be utilized for developing sen-
sitive diagnostic tools and radiotracers.

That started to be recently utilized e.g. 11C-acetate and 18F-fluor-
odeoxyglucose positron emission tomography/computed tomography
dual imaging for the prediction of response and prognosis after trans-
arterial chemoembolization.

Conclusion

We conclude that DCA is an antimetabolite that antagonizes acetate
for vital reactions in cancer cells.

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Conflict of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://

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