Chemical Metabolic Inhibitors For The Treatment Of Blood-Borne Cancers.

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Abstract

Tumor cells, including leukemic cells, remodel their bioenergetic system in favor of aerobic glycolysis. This process is called “the Warburg effect” and offers an attractive pharmacological target to preferentially eliminate malignant cells. In addition, recent results show that metabolic changes can be linked to tumor immune evasion. Mouse models demonstrate the importance of this metabolic remodeling in leukemogenesis. Some leukemias, although treatable, remain incurable and resistance to chemotherapy produces an elevated percentage of relapse in most leukemia cases. Several groups have targeted the specific metabolism of leukemia cells in preclinical and clinical studies to improve the prognosis of these patients, i.e. using L-asparaginase to treat pediatric acute lymphocytic leukemia (ALL). Additional metabolic drugs that are currently being used to treat other diseases or tumors could also be exploited for leukemia, based on preclinical studies. Finally, we discuss the potential use of several metabolic drugs in combination therapies, including immunomodulatory drugs (IMiDs) or immune cell-based therapies, to increase their efficacy and reduce side effects in the treatment of hematological cancers.

Introduction

During the last years, and partially related to the tumor resistance to conventional chemotherapy, basic researchers and clinicians have looked for new protocols to fight cancer. Ten years ago, the "old" idea that the immune system could fight against tumors started receiving special attention [1, 2]. In the same period, new results highlighted the role of metabolism during tumorigenesis [3]. However, forcing metabolic changes in tumors with several drugs in the clinic proved highly toxic, precluding the wide use of some of the so-called metabolic drugs. Nevertheless, it is possible to combine these drugs with approaches of immunotherapy to treat leukemia patients. However, the fact that the effector cells in immunotherapy and leukemic cells share some metabolic pathways indicates that further studies are required to elucidate the correct combination therapies.

Blood-borne cancers

These cancers include mainly three types of diseases: leukemia, lymphoma and myeloma. In these cases, accumulation of tumor cells in blood or in the bone marrow interferes with the production of normal blood cells, generating clinical complications. Leukemia, from the ancient Greek "whiteblood", encompasses several types of disease. In chronic leukemia, typically developed in aged people, the patient expresses elevated levels of white blood cells but the disease progresses slowly. In chronic lymphocytic leukemia (CLL), if possible, treatment starts after a prolonged period of monitoring. In chronic myelogenous leukemia (CML), patients are treated with tyrosine phosphokinase inhibitors after diagnosis. In acute leukemia, there is a rapid increase in tumor cells, which should be treated quickly. The survival rate is lower in acute lymphocytic leukemia (ALL) and acute myelogenous leukemia (AML) compared to CLL and CML, although CLL is still considered as an incurable disease.

Lymphoma is also caused by tumor lymphocytes but is a solid tumor, in contrast to leukemia, and its prognosis is generally better than leukemia. Multiple myeloma (MM) is produced by tumor

plasma cells, and, while incurable, can generally be treated, with a median survival rate of 5 years [4].

The treatment of hematological cancers typically combines multi-component therapy regimens. Some are treated with radiation and/or other approaches, including monoclonal antibodies [5], vaccines [6] or cell therapy [7]. As a last resort, a bone marrow transplant is useful in some cases, although this protocol is hindered by its toxicity. Thus, these patients clearly need new therapeutic approaches. An idea gaining favor is to specifically target tumor cell metabolism [8] without affecting normal cells. This new "family" of metabolic drugs could be used in patients not responding to the standard treatments.

Aberrant metabolism in leukemia

Highly proliferating cancer cells need a constant source of energy and biomolecules for the production of macromolecules. Eukaryotic cells obtain most of their energy via oxidative phosphorylation (OXPHOS), also named respiration. In this process, mitochondria use pyruvate to generate a final amount of 36 molecules of ATP. However, rapidly growing tumor cells remodel their bioenergetic system to favor glycolysis despite the presence of oxygen, which is termed the Warburg effect [9]. In this case, pyruvate is metabolized to lactate to generate 2 molecules of ATP. While the amount of ATP generated in this way is much lower compared to OXPHOS, glycolysis is more rapid and provides cancer cells with necessary macromolecules to fulfill the increased necessities of proliferating cells [3]. The essential role of this metabolic shift in leukemogenesis is demonstrated by mice bearing lysine to arginine mutations at three acetylation sites on p53 (p533KR). The p533KR mutant is functional, as it cannot mediate cell-cycle arrest, senescence and apoptosis; however, mice bearing this construct do not succumb to spontaneous thymic lymphomas, unlike p53 null mice [10]. Importantly, the p533KR mice retain the ability to regulate energy metabolism and reactive oxygen species (ROS) production. These

findings underscore the critical role of metabolic regulation and antioxidant activities in blocking spontaneous leukemogenesis [10]. Consistent with this, certain leukemias, such as AML, show a very high percentage of mutations in genes related to metabolism [11, 12], notably mutations in isocitrate dehydrogenase (IDH1) and IDH2 [13] that stabilize hypoxia-inducible factor 1α (HIF1-α). This metabolic shift specific for tumor cells is observed in leukemic cells of different origins [14-16], and probably promotes the development of the malignancy [11]. Thus, this offers an interesting pharmacological opportunity to selectively target the tumor. The Warburg effect was initially linked to the hypoxic conditions that some tumors encountered during their development. Recently, it has become clear that this effect provides tumors with several growth advantages in their normally adverse environment [17].

In certain cases, AML cells show an atypical Warburg effect. In leukemic cells growing in co-culture with mesenchymal stem cells (MSCs), mitochondrial uncoupling mimics the Warburg effect in cells with high oxidative capacity [14]. In this situation, leukemic cells perform a metabolic shift to fatty acids oxidation (FAO) instead of oxidizing pyruvate. Etomoxir (EX; for a summary of the compounds described in this review: Table 1, Table 2 and Figure 2), a carnitine palmitoyl transferase 1 (CPT1) inhibitor that blocks FAO, sensitizes human AML cells to apoptosis [18]. Moreover, in co-treatment with ABT-737 (an inhibitor of Bcl2 family proteins) or arabinoside (Ara-C), EX delays AML cell growth in xenograft murine model and extends survival of mice[18]. EX is already used in the clinic to treat heart failure by switching cardiac cell energy supply from fatty acids to pyruvate. Inhibition of FAO can also have benefits in other types of leukemia, such as CLL [18] and multiple myeloma [19].

Glutamine metabolism

Researchers working with leukemic cells realized a long time ago that glutamine is required for full proliferation and survival. In fact, leukemic cells consume more glutamine than non-

transformed cells and more than is required for their anabolism [20]. This effect is facilitated by NF-κB activation, which inhibits miR-23 expression and relieves inhibition of glutaminase (GLS) mRNA expression [21]. This provides an additional growth advantage to leukemic cells, which generally have constitutively active NF-κB [22-24]. Hence, in addition to the Warburg effect, leukemic cells show considerably increased glutamine consumption. In the clinic, glutamine metabolism in tumor cells was targeted with glutamine analogs like acivicin and 6-diazo-5-oxo-l-norleucine (DON). However, the toxic effects on the central nervous system precluded further development of these compounds [25].

Glutamine provides proliferating cells with a source of carbon to sustain intermediates of the tricarboxylic acid (TCA) cycle and a source of nitrogen to produce other valuable molecules, such as nucleotides, hexosamines and non-essential amino acids [26]. Glutamine also supports *de novo* synthesis of purines and pyrimidines by supplying amido nitrogen. Transformed cells show a delay in S-phase in low glutamine conditions due to low nucleotide biosynthesis [27]. Glutamine catabolism provides cells with lactate, alanine and ammonia, which are important for maintenance of non-essential amino acid pools. In addition, glutamine metabolism also activates mammalian target of rapamycin (mTOR), which is important for cell growth and autophagy [28]. The pleiotropic role of glutamine in biosynthetic processes could explain the observed toxicity of glutamine analogs.

Inhibitors of glutamine metabolism

As a first step of glutaminolysis, glutamine is metabolized into glutamate by the action of mitochondrial glutaminase GLS. This glutamate is used as anaplerotic and bioenergetic substrate by mitochondria. Cells growing in the presence of glutamine use this pathway to supply substrate to the TCA cycle [29]. When glucose metabolism is impaired, glutamine will be used for growth and cell survival. This alternative pathway of energy in tumor cells makes them resistant to

therapies targeting glucose metabolism or nutrient depletion [30, 31]. In addition, glutamine supports tumorigenesis by other means. The initial stage of tumor cell formation is accompanied by the activation of oncogenes, which leads to production of ROS, triggering cell death or senescence by DNA damage. Glutamine metabolism counteracts ROS by two pathways. First, glutamine provides glutamate and nitrogen for the synthesis of the antioxidant glutathione (GSH). In fact, GSH synthesis is directly related to the availability of glutamine and the activity of GLS [26]. Second, glutamine provides NAPDH, which is necessary to maintain GSH in its reduced state [30]. Certain oncogenes, like c-Myc, increase the metabolism of glutamine by favoring its transport and controlling expression of both GLS and glutamylcysteine synthetase (an enzyme involve in GSH synthesis). Inhibition of GLS prevents Rho GTPase-induced NIH-3T3 cell transformation [32], while, in leukemic Jurkat cells, expression of miR-23 impairs GLS expression and blocks proliferation [21]. Complicating this "classical" model is the fact that the human genome encodes two distinct isozymes of GLS. *GLS1* and *GLS2* encode the kidney-type and the liver-type isoenzymes, respectively, where the latter reportedly has a tumor-suppressing role. p53 activates GLS2 transcription and triggers glutamine metabolism and GSH synthesis, which in turn increases antioxidant activity and contributes to the tumor suppression function of p53 [33, 34].

As described above, glutamine addiction is found in several types of tumors, including leukemic cells [35]. Treatment strategies for pediatric ALL include L-asparaginase (Elspar, [Merck & Co. Inc.], Oncaspar [Enzan Inc.]), an enzyme that hydrolyzes asparagine into aspartic acid, and ammonia [36]. L-asparaginase has enough glutaminase activity to appreciably reduce glutamine levels; its success in the clinic is reasonably explained by glutamine depletion [35, 37, 38]. This offers a clear example of how metabolic changes can be exploited to treat cancer.

Unfortunately, other attempts to specifically target glutamine metabolism has shown poor results: the toxicity of DON and other glutamine analogs precludes their use in the clinic despite their positive effect *ex vivo* or in mouse xenografts [25]. Since GLS is the rate-limiting enzyme in glutamine catabolism, a GLS-specific inhibitor could circumvent this problem, as it should not affect other glutamine roles. It should selectively target GLS1, as GLS2 shows tumor suppressor activity [33, 34]. Based on this idea, bis-2-(5-phenylacetimido-1,2,4,thiadiazol-2-yl)ethyl sulfide (BPTES) was developed as a selective GLS1 inhibitor [39]. It inhibits tumor growth *in vitro* and in animal models and is currently being tested in preclinical studies [40]. There is also the possibility of targeting the next step of glutaminolysis by inhibiting glutamate dehydrogenase (GDH) with epigallocatechin gallate, which sensitizes tumor cells to glucose deprivation [41]. However, the *in vivo* effect of this drug should be more carefully studied [42].

From glycolysis to oxidative phosphorylation (OXPHOS)

The characteristics unique to tumor cell metabolism offer the possibility of specifically targeting it. Below we present several approaches that have already reached the clinic and that might be combined with immunotherapy. One enzyme implicated in tumor metabolic remodeling and whose expression is regulated by oncogenic transcription factors is pyruvate dehydrogenase kinase 1 (PDK1), [3]), which is inhibited by dichloroacetate (DCA). PDK1 inhibition leads to pyruvate dehydrogenase (PDH) activation and forces cells to use mitochondria as the main ATP generator. As a result, glycolysis is vastly diminished. Several clinical studies have shown the efficacy of DCA in lowering lactate levels [43]. It can be used for treating lactic acidosis with a relatively high oral dose of 25-100 mg/Kg of body weight. DCA is used in USA for the treatment of several metabolic diseases and is currently in clinical trials for the treatment of cancers, notably glioblastoma [44]. Moreover, at least one patient with non-Hodgkin's lymphoma was cured using DCA as an auto-medication [45]. The patient showed a minimal peripheral neuropathy that was resolved upon co-treatment with thiamine. Finally, DCA conjugated to

hemoglobin can be specifically directed to the monocytic cancer cell line THP-1, where it inhibits tumor cell growth [46]. However, it should be noted that DCA is not currently in clinical trial for treating leukemia, although it is widely used as an automedication.

Another target enzyme implicated in metabolism is AMP-activated protein kinase (AMPK), which is an important sensor of intracellular energy levels. AMPK targets acetyl CoA carboxylase (ACC), FASN, mTORC1 (mTOR Complex I) and p53, thereby inducing oxidative metabolism, propelling fatty acid oxidation and inhibiting ATP-consuming anabolism. Thus, AMPK mainly plays an anti-tumor role [47]. Moreoever, AMPK is linked to stress resistance and survival in conditions of metabolic stress, at least in non-hematopoietic tumor cells [48, 49]. In contrast, the AMPK activating kinase liver kinase B1 (LKB1) shows loss of function in several cancers and is generally considered a tumor suppressor [50].

In hematopoietic cells, the LKB1/AMPK axis plays a similar role as in other tissues but it also regulates additional T cell-specific activities, such as development, homeostasis and effector functions [51]. AMPK negatively regulates the Warburg effect in leukemic cells and conversely, genetic ablation of AMPK accelerates Myc-induced lymphomagenesis [52]. This suggests that activating the LKB1/AMPK pathway could be a novel strategy for treating leukemia [53].

Patients suffering from metabolic syndrome and type 2 diabetes and treated with the AMPK activator metformin show reduced incidence of cancer [47]. Based on this, the Nobel Prize winner Dr. James Watson is using it as an automedication against prostate cancer (http://www.utsandiego.com/news/2013/mar/21/nobel-watson-DNA-irish/). Metformin treatment of mice harboring naturally arising lymphomas or cancer xenografts delays tumorigenesis [54, 55]. Given the results described above and that hyperglycemia is associated with a poor outcome in ALL after chemotherapy [56], several groups have tested the effect of metformin on leukemic cells. Metformin induces apoptosis and autophagy in T-ALL cell lines [57] and improves chemosensitivity in ALL primary tumor samples [58]. It also suppresses CML precursors in

BCR-ABL-expressing cells [59] and reduces the growth of AML cells in nude mice without affecting normal hematopoiesis, at least *ex vivo* [60]. Finally, metformin is being tested against leukemia in a clinical trial (NCT01324180) sponsored by the H. Lee Moffitt Cancer Center and Research Institute. Metformin is being used together with vincristine, dexamethasone, doxorubicin, and PEG-asparaginase (VPLD) to treat relapsed childhood ALL. Whereas all this information is clinically relevant, it should be noted that metformin is primarily a mitochondrial complex I inhibitor that mainly activates AMPK through a decrease in ATP levels and increase in AMP levels [61].

An important partner of AMPK is the tumor suppressor p53, which is emerging as an important regulator of metabolic homeostasis [62]. p53 mainly functions as a transcription factor controlling the expression of multiple genes; interestingly, it also participates in the maintenance of mitochondrial health and activity. Since p53 promotes OXPHOS and inhibits glycolysis [63], therapies that reactivate wild type p53 might contribute to maintain mitochondrial respiration and restrain the Warburg effect in tumor cells.

More than 50% of all tumors contain mutations in the *p53* gene. Many p53 mutations cause gain of function and thereby enhance tumorigenesis and therapy resistance. Mutant p53 promotes aerobic glycolysis by activating the expression of hexokinase-2 (HK2)[64]., Nevertheless, p53 mutations are less frequent (10 to 15%) in hematological malignancies than in solid tumors [65, 66]. However, p53 mutations increase during disease progression and also in response to chemotherapy. For instance, there is a strong association between therapy and the increase in novel p53 abnormalities in CLL [67], with p53 mutations linked to a poor clinical outcome, disease progression and drug resistance in AML and in B-cell CLL. Small molecules, notably PRIMA-1 and ellipticine, revert mutant p53 by restoring the active conformation and DNA binding[68, 69], leading to p53-dependent suppression of tumor cell growth *in vitro* and *in vivo*. PRIMA-1 increases the efficacy of AML treatment in patients with p53 mutations [70], while

Ellipticine sensitizes chemoresistant lymphoma cells to doxorubicin treatment [71]. Other strategies disrupt the interaction of mutant p53 with key partners, e.g. the high levels of mutant p53 in several cancer cell lines are due to its interaction with heat-shock protein 90 (Hsp90). This protects mutant p53 from Mdm2-mediated ubiquitination and proteasomal degradation. The ATP analogue 17-Allylamino-17-demethoxygeldanamycin (17-AAG) inhibits the function of HSPs and is currently in clinical trials, including blood-borne cancers (NCT00117988). 17-AAG–mediated Hsp90 inhibition allows the E3 ligases Mdm2 and CHIP to ubiquitinate and degrade mutant p53 [72]. Therefore, targeting mutant p53 could be an attractive approach as a novel cancer therapy that would affect tumor cell metabolism.

Histone deacetylases

Aberrant histone deacetylase (HDAC) activity is commonly observed in leukemia cells, causing increased proliferation and resistance to apoptosis through transcriptional silencing of critical genes, such as the cyclin-dependent kinase inhibitor $p21^{WAF1}$ and the transcription factor E2F-1 [73-75]. HDAC inhibitors are already in the clinic to treat hematological cancers: Vorinostat or suberoylanilide hydroxamic acid (SAHA; trade name Zolinza) and Romidepsin (trade name Istodax) have been licensed by the U.S. FDA for the treatment of cutaneous T cell lymphoma (CTCL) and the last is being tested in phase II in other hematological diseases such as MM and peripheral T-cell lymphoma. In addition, HDAC8 inhibitors could be useful to treat T-cell lymphomas [76], especially if more potent and specific inhibitors could be developed [77, 78].

Sirtuins

Recently, sirtuins, particularly Silent mating type information regulation 2 homolog1 (Sirt1), have been proposed to play an important role in leukemogenesis [79]. This class III histone deacetylase controls cell metabolism by activating both the nuclear receptor peroxisome

proliferator-activated receptor (PPAR) and the transcription coactivator PPARγ (PPARG) coactivator-1alpha (PGC-1α also known as PARGC1A)[80]. PGC1α interacts with the transcription factors Nuclear Respiratory Factor 1 (NRF1) and NRF2 to induce expression of mitochondrial genes [80]. NRF1 activates the transcription of some key metabolic genes. It also regulates the expression of cell growth and nuclear genes required for respiration, heme biosynthesis and mitochondrial DNA transcription and replication, whereas NRF2 activates anti-oxidant genes [81]. Sirt1 has been shown to increase lifespan in yeast, worms and flies [82]. Sirt1 is overexpressed in many types of cancers, including the leukemias AML, CLL and CML [83-85]. This strongly suggests a role for Sirt1 in proliferation of this kind of tumor cells. Accordingly, Sirt1 inhibitors lead to growth arrest and apoptosis in leukemic cells, where chemoresistant cells have increased Sirt1 levels [86, 87]. The Sirt1 inhibitor Tenovin-6 [88] reduces tumor growth by increasing p53 acetylation and transcription activity in CML stem cells [85]. Salermide, another Sirt1 inhibitor, causes apoptosis in several leukemic cell lines [89]. Further studies with derivatives of Salermide demonstrated an anti-proliferative and/or apoptotic effect in several cancer cell lines, including leukemia [90]. These promising results suggest that Sirt1 inhibitors may be beneficial in treating leukemia. This optimism is tempered by the fact that Sirt1 is required for the beneficial effect of the polyphenol resveratrol on mitochondrial function in mice [91]. Moreover, resveratrol can induce apoptosis in human B-CLL [92] and in MOLT-4 acute lymphoblastic leukaemia cells [93]. Hence, activation of Sirt1 could play an anti-tumor role. Thus, any strategy targeting Sirt1 should be carefully considered before its use in the clinic.

Immune surveillance

One major reason for the inefficacy of selective enzyme inhibitors as anticancer drugs is the sophistication of the system that regulates metabolism. Selective blockade of a single enzyme induces changes of metabolism and transport of molecules that can compensate for the deficit.

This system clearly undergoes a massive remodeling during tumorigenesis, which may also be tumor specific [94, 95] and undergo alteration during progression [96]. Importantly, the altered metabolic state of tumors provides several advantages beyond the increase in "bricks" for anabolism [8], notably the ability to avoid the immune response [8]. Immune cells are prepared to attack and destroy tumor cells, which defend themselves by blocking immune effector cells or becoming invisible to them. In cancers, it is clear that tumor cells have used at least one of these strategies. Therefore, one possible way to attack tumor cells would be to reverse their tumor phenotype, thereby compromising both proliferation and immune evasion.

The immune system is primarily devoted to protect the host from several dangers, such as foreign antigens, which include tumor-associated antigens (TAAs). The "cancer immunosurveillance" hypothesis, initially proposed by Burnet and Thomas, maintains that the immune system protects the host from tumorigenesis [97]. Hence, the immune system is continuously on patrol to recognize and destroy nascent tumors [1]. However, the constant pressure exerted by the immune system promotes the emergence of tumors with reduced immunogenicity that can escape immune attack [2, 98, 99]. Hence, anti-tumor immunotherapy must overcome the poor immunogenicity of tumor cells. Two main strategies are possible: using immune cells in an activated state that overcome the lack of positive signals coming from the tumor cells or increasing tumor cell immunogenicity with specific antibodies that bind to tumor cell antigens and produce Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC;[8]). The two main arms are the adaptive and the innate immune system. To eliminate tumor cells, the adaptive immune system recognizes foreign antigens presented by the MHC-I complex on the surface of target cells. The main effector cells therein are $CD8^+$ cytotoxic T lymphocytes (CTLs). The T-cell receptors of these cells recognize and bind to the MHC-I complex, the equivalent to the host "identity card" and considered as the self-molecule. When "modified" by the presence of a foreign antigen, it triggers the CTLs to attack. It is now clearly established that this system can also attack and eliminate tumor cells

because they express *de novo* antigens that are recognized as non-self [1, 2]. In the innate immune system, one of the main effector cells is the natural killer (NK) cell, which recognizes the absence of MHC-I [100]. This lack, along with the expression of stress molecules in the surface of target cells, triggers NK cell attack. Through this mechanism, pathogens cannot escape from the immune system simply by down regulation of MHC-I expression [100]. *In vivo*, the immune system can eliminate both MHC-I expressing [98] and non-expressing [101] leukemic cells. To avoid recognition by effector immune cells, tumor cells use tactics similar to those used by viruses, which target proteins implicated in MHC-I expression and antigen presentation machinery (APM); [102]. This allows tumors to greatly decrease or eliminate the expression of TAAs [103]. The molecular mechanisms underlying abnormal expression of MHC-I in mice and its equivalent in humans, known as human leukocyte antigen (HLA), include mutations or epigenetic changes in the genes encoding the HLA class I heavy chain, MHC-I light chain β2-microglobulin (β2m) and APM [104]. The expression of one or more of these proteins is often altered in tumor cells, leading to a decrease of MHC-I surface expression. These alterations are found in a majority of cancers and prevent anti-tumor adaptive immune response by avoiding CTLs attack[103, 104]. To escape recognition by NK cells, tumor cells maintain a low level of surface MHC-I expression[100, 105]. Thus, two important subsets of immune cells in charge of killing tumor cells are influenced by the level of MHC-I at the cell surface.

Immunomodulatory drugs

Significant efforts are underway to stimulate the anti-tumor activity of effector immune cells and have led to the "rediscovery" of the immunomodulatory drugs (IMiDs). The principal IMiDs are thalidomide, lenalidomide and pomalidomide. They have immunomodulatory and antiangiogenic activities, and can act directly on tumor cells. Thalidomide and lenalidomide were first approved for multiple myeloma (MM), while lenalidomide is used for myelodysplastic syndrome (MDS).. Moreover, these drugs are effective against other hematologic malignancies.[106]. Pomalidomide

shows promising results in clinical trials, either alone or combined with other drugs like dexamethasone, prednisone or cyclophosphamide. [107] Although several mechanisms have been proposed to explain the activity of IMiDs in multiple myeloma (MM), cereblon (CRBN), a ubiquitously expressed E3 ligase protein, is likely its primary target and would explain thalidomide teratogenicity [108]. One target of CRBN is interferon regulatory factor 4 (IRF4), which is critical for myeloma cell survival and is down regulated by IMiDs treatment [109]. IMiDs stimulate NK, $CD8^+$ and $CD4^+$ effector cells, whereas they inhibit T regulatory (Treg) cells [110].

OXPHOS induces MHC-I expression

Tumor metabolism can adapt to the environment and can vary between patients with the same disease [96]. It seems very likely that the tumor metabolism observed *ex vivo*, or after culturing cells *in vitro*, is just a small picture of what happened in the process of tumorigenesis. When glycolysis is inhibited, cells use alternative energy substrates, such as glutamine. Glutaminolysis generates ATP through OXPHOS [29, 111] and leukemic cells forced to perform OXPHOS increase MHC-I expression at the cell surface [31, 112] via a pathway regulated by extracellular signal-regulated kinase-5 (ERK5) [31, 113]. ERK5 plays an important role in leukemic T cell survival through activation of the NF-κB pathway [114, 115], and ERK5 inhibition blocks multiple myeloma tumor cell proliferation and induces apoptosis *in vitro* and *in vivo* mouse models [116]. In contrast, inhibition of OXPHOS reduces MHC-I expression, suggesting that inhibitors of GLS would decrease MHC-I expression. This idea remains to be proven formally.

While a large fraction of drugs aim to stimulate immune effector cells, there is also the possibility of sensitizing cancer cells to the immune system. An obvious target is MHC-I expression, which is reduced in most tumors [103]. Changing tumor cell metabolism to OXPHOS should induce MHC-I expression [31, 112] and, in consequence, presentation of TAAs. In addition, metabolic

drugs may directly affect tumor cell survival, inducing some cell death as observed with metformin and DCA [31, 112]. This should facilitate the uptake of TAAs by dendritic cells that, after migrating to the draining lymph nodes, would generate an effective immune response by activating $CD4^+$ Th1 and $CD8^+$ cells. The metabolic drugs would also increase MHC-I expression in tumor cells, thus facilitating their recognition by specific CTLs (Figure 1). The metabolic drugs DCA and metformin, which are already in the clinic and have shown efficacy against certain tumor cells, induce OXPHOS and an increase in MHC-I expression [31, 112]. It remains to be established whether their clinical efficacy is linked to the activation of an antitumor immune response. We would predict that, in patients that express low MHC-I levels with non-hard lesions in their MHC-I expression machinery [103], DCA or metformin treatment could increase MHC-I expression, thereby making tumor cells more visible to CTLs by increasing presentation of TAAs.

Association of metabolic drugs with CTLs and/or NK cell infusion: is there a possibility?

Cancer patients are usually immunosuppressed due to the disease or treatment. To boost the antitumor activity of their immune system, modulators of glutamine metabolism, like DCA and/or metformin could be used in combination with immune cell transplantation to treat patients resistant to standard therapies. Here, we speculate on several possibilities that have not yet been attempted in the clinic (explained in figure 1).

Drugs that induce an increase in MHC-I expression could be combined with an adoptive cell transfer (ACT) by selecting T lymphocytes with antitumor activity. These lymphocytes should be expanded and/or activated *ex vivo* before reinfusion into the patient. In most cases, patients received classical lymphodepleting regimens based on cyclophosphamide plus fludarabine, either alone or in combination with total body irradiation. In addition, patients are treated with high doses of interleukin 2 (IL-2) to favor lymphocyte proliferation (for a specific review of clinical trials using these procedures, see [117]). These T cells must be autologous, either selected by or

manipulated for the expression of tumor-specific T-cell receptors [117]. Given our current knowledge, CTLs should be infused into patients several days after treatment with the selected metabolic drug, because it takes several days for DCA or metformin to affect MHC-I expression [31, 112].

NK cells have an important advantage: it is possible to use heterologous cells [100]. NK cells will attack tumor cells lacking an appropriate level of MHC-I and expressing stress markers at the surface. It would be interesting to identify the metabolic drugs that induce stress molecules in leukemic cells, allowing them to activate NK cells. For example, T cells become targets for NK cells after activation because they express ligands of the NK cell activating receptor DNAX accessory molecule-1 (DNAM-1) through a ROS-mediated pathway [118]. Metabolic drugs affect ROS homeostasis and activated T cells show similar metabolism to leukemic cells [20, 119]. Thus, metabolic drugs might sensitize leukemic cells to NK cells.

Metabolic drugs affecting MHC-I expression could also be associated to systemic administration of immunostimulatory agents, such as IMiDs or interleukin-2 (IL-2), which activates both CTLs and NK cells *in vitro* and *in vivo*. If metformin and/or DCA are able to increase expression of MHC-I or stress molecules in a tumor-specific manner, IMiDs or IL-2 should activate CTL or NK cell activity, leading to a more efficient removal of tumor cells (Figure 1).

Conclusions

Mutations in oncogenes and tumor suppressor genes are responsible for the metabolic changes specific to leukemic cells. Metabolic transformation is indispensable for cancer cells to proliferate, survive, develop drug resistance and escape the immune system. Pre-clinical evidence supports the idea that metabolic drugs could prevent hematological cancers. Certain drugs, namely DCA and etomoxir, can easily reach the clinic because they have already been used in humans. Others are in clinical trials or already in the clinic for the treatment of leukemias:

metformin, L-asparaginase and 17-AAG. It is important to test if these drugs can synergize with immunomodulators, such as ImiDs, or with adoptive cell therapy (summary in Table 1 and Table 2).

Immunometabolism is an emerging area of research that could prevent or cure many diseases, such as cancer, obesity, diabetes and atherosclerosis. New technological advances will allow the characterization of the metabolic profiles of individual hematological cancer patients, which could lead to personalized treatment strategies. However, additional studies are required to fully understand leukemic cell metabolism and thereby identify new targets and develop more effective cancer therapies with less toxic effects. The goal is to discover new metabolic drugs that will improve the response to therapy and result in a positive clinical outcome.

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Table 1. Metabolic drugs, Immunomodulators and related compounds for hematological cancer treatment.

	Compounds	Target	Effect
Metabolic drugs	Etomoxir	Carnitine palmitoyl transferase 1	Block of fatty acid oxidation
	Tenovin-6	Sirt1	Increase of p53 transcriptional activity
	Salermine	Sirt1	Increase of mitochondrial biogenesis
	Resveratrol	Sirt1	Stimulate lipolysis
	Acivicin	Gamma-glutamyl transpeptidase	Inhibition of glutamine metabolism
	DON	Glutamine	Inhibition of glutamine metabolism
	BPTES	Mitochondrial glutaminase	Specific inhibition of GLS1
	Epigallocatechin gallate	Glutamate dehydrogenase	Inhibition of glutaminolysis
	DCA	PDK1	Increase of OXPHOS and MHC-I expression
	Metformin	AMPK	Increase of OXPHOS and MHC-I expression
Immuno-modulators	Thalidomine	Cereblon	Activation of T cells and stimulation of NK cell cytotoxicity
	Lenalidomine	Cereblon ,Tumor necrosis factor?	Activation of T cells and stimulation of NK cell cytotoxicity
	Pomolidomine	Cereblon	Up-regulation of Interferon gamma, IL-2 and IL-10
Additional compounds	PRIMA-1	Mutant p53	Reactivates the function of mutant p53
	Ellipticine	Mutant p53	Reactivates the function of mutant p53
	17-AAG	Hsp90 inhibitor	Increase degradation of mutant p53

DON, 6-diazo-5-oxo-l-norleucine; BPTES, bis-2-(5-phenylacetimido-1,2,4,thiadiazol-2-yl)ethyl sulfide; GLS1, glutaminase type 1; DCA, dichloroacetate; PDK1, pyruvate dehydrogenase kinase 1; OXPHOS, oxidative phosphorylation; MHC-I, Major histocompatibility complex; AMPK, AMP-activated protein kinase; NK, Natural Killer cells; PRIMA-1, p53 re-activation and induction of massive apoptosis; 17-AAG, 17-*N*-Allylamino-17-demethoxygeldanamycin.

Table 2. Molecular weight and empirical formula of Metabolic drugs, Immunomodulators and related compounds for hematological cancer treatment.

Product	Molecular Weight	Empirical Formula
17-AAG	585.69	$C_{31}H_{43}N_3O_8$
acivicin	178.57	$C_5H_7ClN_2O_3$
L-asparaginasa	≈136000	Enzyme Commission (EC) Number 3.5.1.1
BPTES	524.68	$C_{24}H_{24}N_6O_2S_3$
DCA (dichloroacetate)	150.92	Cl_2CHCO_2Na
DON	171.15	$C_6H_9N_3O_3$
Ellipticine	246.31	$C_{17}H_{14}N_2$
Epigallocatechin gallate	458.37	$C_{22}H_{18}O_{11}$
Etomoxir (sodium salt)	338.76	$C_{15}H_{18}ClO_4 \cdot Na \cdot H_2O$
Lenalidomide	259.3	$C_{13}H_{13}N_3O_3$
Metformin hydrochloride	165.62	$C_4H_{12}ClN_5$
Pomalidomide	273.24	$C_{13}H_{11}N_3O_4$
PRIMA-1	185.22	$C_9H_{15}NO_3$
Resveratrol	228.24	$C_{14}H_{12}O_3$
Salermide	394.47	$C_{26}H_{22}N_2O_2$
Tenovin-6	454.6	$C_{25}H_{34}N_4O_2S$
Thalidomide	258.23	$C_{13}H_{10}N_2O_4$

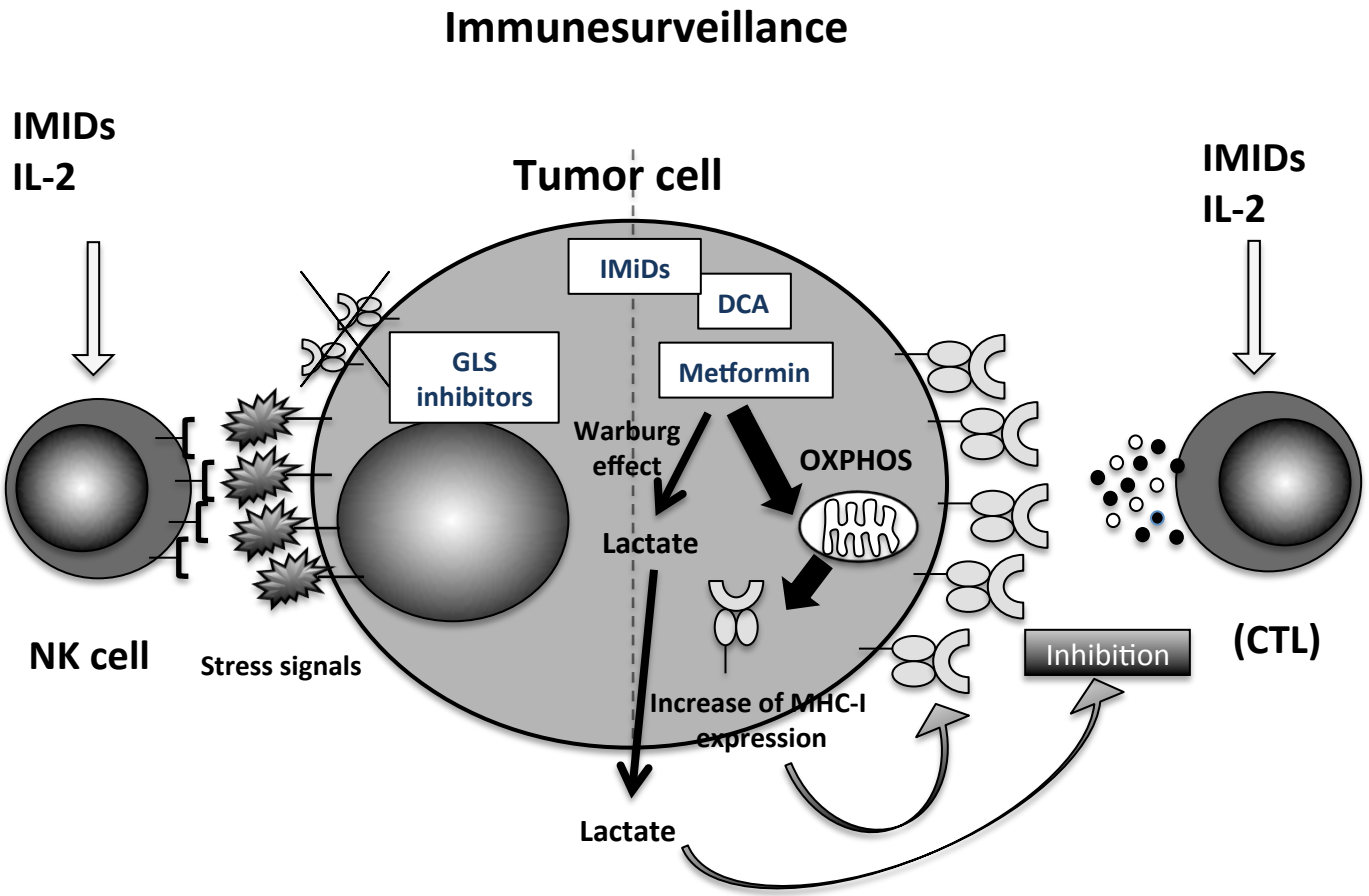

Figure 1. Co-regulation of metabolism and immune function to kill tumor cells. Metabolic drugs such as DCA and Metformin induce OXPHOS that up-regulate the MHC-I expression, immunomodulators (IMiDs) and IL-2 stimulate the anti-tumor activity of effector immune cells (CTL and NK cells). This strategy will help the CTLs to recognize and bind to the MHC-I complex. In contrast, inhibition of OXPHOS reduces MHC-I expression and Natural Killer cells (NK) will recognize the absence of MHC-I and the stress signals. GLS inhibitors could induced NK activation by these means.