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Expression and/or activity of the SVCT2 ascorbate transporter may be decreased in many aggressive cancers, suggesting potential utility for sodium bicarbonate and dehydroascorbic acid in cancer therapy ☆

Mark F. McCarty *

NutriGuard Research, 1051 Hermes Ave., Encinitas, CA 92024, United States

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ABSTRACT

Hypoxia-inducible factor-1 (HIF-1) is a heterodimer transcription factor whose elevated activity in many cancers helps them to survive under hypoxic conditions and enhances their capacity to grow invasively, establish metastases, and survive chemo- or radiotherapy. Optimal intracellular levels of ascorbate suppress the level and transcriptional activity of HIF-1under normoxic or mildly hypoxic conditions by supporting the activity of proly and asparagyl hydroxylases that target HIF-1alpha. High intracellular ascorbate can also work in various ways to down-regulate activation of NF-kappaB which, like HIF-1 is constitutively active in many cancers and promotes aggressive behavior – in part by promoting transcription of HIF-1alpha. Yet recent evidence suggests that, even in the context of adequate ascorbate nutrition, the intracellular ascorbate content of many aggressive cancers may be supoptimal for effective HIF-1 control. This likely reflects low expression or activity of the SVCT2 ascorbate transporter. The expression of SVCT2 in cancers has so far received little study; but the extracellular acidity characteristic of many tumors would be expected to reduce the activity of this transporter, which has a mildly alkaline pH optimum. Unfortunately, since SVCT2 has a high affinity for ascorbate, and its activity is nearly saturated at normal healthy serum levels of this vitamin, increased oral administration of ascorbate would be unlikely to have much impact on the intracellular ascorbate content of tumors. However, cancers in which HIF-1 is active express high levels of glucose transporters such as GLUT-1, and these transporters can promote influx of dehydroascorbic acid (DHA) via facilitated diffusion; once inside the cell, DHA is rapidly reduced to ascorbate, which effectively is "trapped" within the cell. Hence, episodic intravenous infusions of modest doses of DHA may have potential for optimizing the intracellular ascorbate content of cancers, potentially rendering them less aggressive. Indeed, several published studies have concluded that parenteral DHA – sometimes in quite modest doses – can retard the growth of transplanted tumors in rodents. As an alternative or adjunctive strategy, oral administration of sodium bicarbonate, by normalizing the extracellular pH of tumors, has the potential to boost the activity of SCTV2 in tumor cells, thereby promoting increased ascorbate uptake. Indeed, the utility of oral sodium bicarbonate for suppressing metastasis formation in nude mice xenografted with a human breast cancer has been reported. Hence, oral sodium bicarbonate and intravenous DHA may have the potential to blunt the aggressiveness of certain cancers in which suboptimal intracellular ascorbate levels contribute to elevated HIF-1 activity.

A key role for intracellular ascorbate acid in control of HIF-1 acitivity

The HIF-1 transcription factor (hypoxia-inducible factor-1) is highly active in many cancers, even under aerobic conditions, and boosts the synthesis of a wide range of proteins that promote invasion, metastasis, and resistance to apoptosis (and hence resistance to chemotherapy or radiation) [1–7]. Strong activation of HIF-1 in hypoxic tumor regions is believed to be largely responsible for the adverse impact of tumor hypoxia on prognosis, and for the less than spectacular longer-term clinical results with the anti-angiogenic cancer drugs developed to date. The activity of HIF-1, a heterodimer, is largely dependent on the nuclear level of its constituent HIF-1alpha, and on post-translational modifications of this protein. In normoxic healthy tissues, the levels of HIF-1alpha are extremely low, as adequate oxygen availability enables its rapid proteasomal degradation. (Hence it is "hypoxia-inducible"). This degradation is contingent on adequate intracellular levels of ascorbate.

Intracellular ascorbate functions to support the activity of prolyl and aspargyl hydroxylases which regulate the catabolism and

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* Tel.: +1 760 216 7272.
E-mail address: markfmccarty@gmail.com

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transactivational activity of HIF-1alpha. Prolyl hydroxylase-2 (PHD2) hydroxylates two proline residues on this protein (Pro402 and 562 in humans); these hydroxylations enable an E3 ligase complex containing von Hippel–Lindau protein (pVHL) to recognize HIF-1alpha and target it for proteasomal degradation [8–10]. The asparaginyl hydroxylase FIH (factor inhibiting HIF) targets asparagine 803 for hydroxylation, thereby preventing effective interaction between the HIF-1 heterodimer and its coactivator p300/CBP, and hence suppressing HIF-1-driven transcription [11]. Molecular oxygen and alpha-ketoglutarate are obligate substrates for these hydroxylation reactions; this requirement for oxygen explains why HIF-1 levels and activity are typically elevated in severely hypoxic cells. Additionally, a ferrous iron atom in the active site of these hydroxylase enzymes plays a crucial catalytic role. This ferrous atom is susceptible to oxidation to ferric valence by hydrogen peroxide and other oxidants; ascorbate promotes the activity of these HIF-1 hydroxylases by efficiently reversing oxidation of their active site iron atoms [12–18].

The transcriptional activity of HIF-1 heterodimers is frequently elevated in aggressive cancers, even in cells that are adequately oxygenated. This can reflect increased translation of HIF-1alpha mRNA, owing to activation of the PI3K-Akt-mTor signaling pathway; increased transcription of the HIF-1alpha gene mediated by NF-kappaB; and a serine phosphorylation of HIF-1alpha by p42/44 MAP kinases that promotes its nuclear localization [6].

But HIF-1 hydroxylase activities are also often blunted in cancer cells, even under aerobic conditions, primarily owing to increased oxidation of their catalytic iron atoms [16,19,20]. Increased cellular generation of oxidants, and hence hydrogen peroxide, often contributes to this effect. Constitutive activation of NADPH oxidase complexes has been observed in many cancers, and hypoxia (as opposed to frank anoxia) somewhat paradoxically boosts superoxide production by complex III of the mitochondrial respiratory chain [21–25]. Indeed, when mitochondrial oxidant generation is suppressed in cells subjected to moderate hypoxia (e.g., 1.5% O2), the activity of PHD2 is almost fully restored, reflecting the high affinity of this hydroxylase for O2 [20]. Hydrogen peroxide levels can also be increased in cancer cells whose expression of catalase or glutathione peroxidase is diminished [21].

Another phenomenon which commonly promotes oxidation of the ferrous iron in PHD2 in cancer cells is an elevation of intracellular pyruvate. Pyruvate can interact with the active site of PHD2 in the pocket that functions to bind alpha-ketoglutarate; this somehow promotes sustained oxidation of the active site iron, perhaps by stabilizing the ferric configuration [19,26]. (Somewhat surprisingly, an increased concentration of alpha-ketoglutarate does not counteract this effect; however, succinate is a competitive antagonist of alpha-ketoglutarate in PHD2, for which reason alpha-ketoglutarate administration can promote PHD2 activity in rare tumors with succinate dehydrogenase deficiency [27]). In cancer cells with elevated HIF-1 activity, increased expression of glucose transporters, glycolytic enzymes, and pyruvate dehydrogenase kinase-1 (which catalyzes a phosphorylation that inhibits pyruvate dehydrogenase activity) activates glycolysis while inhibiting mitochondrial oxidation of pyruvate – a phenomenon known as the Warburg effect, responsible for the extracellular acidity of many aggressive cancers [3,6,28]. The resulting elevation of cellular pyruvate tends to suppress PHD2 activity, thereby boosting the half-life of HIF-1alpha and helping to maintain the elevated activity of HIF-1 that underlies this phenomenon – a vicious cycle that sustains the malignant behavior of many cancers.

Fortunately, studies have demonstrated that optimal intracellular concentrations of ascorbate can largely abrogate the adverse impact of oxidative stress and elevated pyruvate on HIF-1 hydrolase activities; an increase in glutathione level may also be somewhat protective in this regard [13,15,17,18]. It is notable that ascorbate can substantially offset the increased HIF-1 activity associated with moderate hypoxia, as this increased activity is mediated primarily by oxidative stress, rather than by inadequate availability of O2 for hydroxylase activity.

Intracellular ascorbate can also down-regulate NF-kappaB activity

Like HIF-1, NF-kappaB is constitutively active in many cancers, and works in a number of ways to make cancers more aggressive and difficult to kill [29,30]; one of these ways is to promote transcription of the gene for HIF-1alpha [31]. There appear to be several ways in which high intracellular levels of ascorbate can suppress NF-kappaB activation. In high intracellular concentrations that can be achieved by pre-loading with dehydroascorbic acid (as discussed below), ascorbate can impede cytokine-triggered signaling pathways that activate NF-kappaB [32]. For example, in ascorbate-loaded cells (4 mM), the ability of TNFalpha to activate NF-kappaB inducing kinase (NIK) is suppressed. This effect presumably reflects a role for induced oxidant production in TNFalpha signaling, as thiol antioxidants exert a similar effect [33–36]. Secondly, the dehydroascorbic acid produced within ascorbate-loaded cells can interact directly with IkappaB kinase-beta (IKKβ) – directly upstream from IkappaB in the canonical pathway of NF-kappaB activation – to block its kinase activity; this effect becomes significant when intracellular ascorbate is relatively high (4 mM) [37]. Finally, there is some evidence that prolyl hydroxylases – notably prolyl hydroxylase 1 – can impede the activation of IKKβ by hydroxylating a key proline in this kinase [38]. By helping to sustain prolyl hydroxylase 1 activity during mild hypoxia or oxidative stress, intracellular ascorbate may thereby help to prevent upregulation of NF-kappaB activity in hypoxic or oxidatively-stressed cancer cells. Indeed, inhibition of prolyl hydroxylase activity appears to be one of the mechanisms whereby hypoxia stimulates NF-kappaB activity.

Ascorbate-mediated inhibition of NF-kappaB activity, by suppressing transcription of HIF-1alpha, can markedly decrease HIF-1 activity, as recently demonstrated by Kawada and colleagues in a human leukemic cell line (K562) with a high capacity for transporting and concentrating ascorbate [39].

Is ascorbate transport suboptimal in many cancers?

These considerations suggest that supplemental ascorbate could be useful in cancer management. But unfortunately, except in individuals whose baseline ascorbate nutritional status is very poor, an increased oral intake of vitamin C, or even intravenous administration of ascorbate, is unlikely to have a major impact on the intracellular vitamin C content of most cancers. Intracellular uptake of ascorbate is mediated by the transporters SCTV1 and SCTV2; these co-transport ascorbate with sodium, and, since extracellular sodium levels are high owing to sodium pump activity, these transporters can concentrate ascorbate against a gradient, maintaining millimolar concentrations of ascorbate in many cells despite typical serum concentrations of 40–80 μM [40–43]. SCTV1 is expressed in a limited range of cells that participate in intestinal ascorbate uptake, renal ascorbate retention, or transport of ascorbate throught the blood–brain barrier; it has a relatively low affinity for ascorbate, but a high capacity for ascorbate transport; hence, its transport activity tends to increase with increasing ascorbate concentrations. The SVCT2 transporter is much more ubiquitously expressed, and is the transporter most commonly found in cancer cells. SVCT2 has a relatively high affinity for ascorbate, with a Km (estimated at 10–30 μM) that is below the range of normal healthy serum concentrations of this vitamin; this implies that elevating

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serum ascorbate levels will have only a modest impact at best on intracellular ascorbate uptake via SVCT2 [43]. (Conceivably, this explains why high-dose oral administration of vitamin C failed to influence cancer progression in two widely publicized randomized controlled studies [44,45]). The characteristic intracellular ascorbate level of a tissue is largely contingent on the degree to which it expresses SVCT2.

Surprisingly, little if any published research to-date has examined the propensity of various human cancers to express SVCT2. Nonetheless, there is recent evidence that intracellular ascorbate levels of human cancers in situ may often be suboptimal for supporting effective HIF-1 hydroxylase activities. Vissers and colleagues recently examined frozen samples of a range of human endometrial cancers, and found that higher grade cancers tended to have lower ascorbate levels than normal endometrial tissue, and that these lower ascorbate levels tended to correlate with increased HIF-1 activity, as assessed by tissue levels of certain proteins (VEGF, GLUT-1, BNIP3) whose synthesis is boosted by HIF-1-mediated transcription [46]. The data suggested that FIH activity was more compromised than PHD2 activity by low ambient ascorbate levels, presumably reflecting a lower affinity of FIH for ascorbate.

That SVCT2 expression and/or activity may sometimes be compromised in cancers is also suggested by a study evaluating intracellular uptake of a radioiodinated derivative of ascorbic acid by adrenal tissue (which avidly assimilates vitamin C in support of steroid and catecholamine synthesis) and two cancers derived from adrenal tissue [47]. Whereas the adrenal glands of nude mice concentrated this radioiodinated derivative quite efficiently, little discernible uptake was noted in the adrenal cancers implanted in these mice. A deficit of SVCT2 expression in the cancers is a likely explanation for this observation.

Furthermore, even in cancers which do not down-regulate SVCT2 expression, a moderate reduction in SVCT2 *activity* in tumors manifesting the Warburg effect can be anticipated. SVCT2 has a mildly alkaline pH optimum of 7.5, reflecting the fact that protonation of one or more histidine residues (pKa = 6.5) of SVCT2 decreases its activity. Indeed, its activity is about 70% lower at pH 6.5 than at pH 7.5 [40]. It is well known that the extracellular pH of many tumors – particularly those in which elevated HIF-1 activity is boosting lactate production – is mildly acidic, to a degree that could be expected to meaningfully compromise SVCT2 activity [48–50]. Importantly, acidity does not influence the affinity of SVCT2 for ascorbate, which implies that an increase in serum ascorbate level could not be employed to counteract this phenomenon [43]. Hence, it is intriguing to speculate that extracellular acidity, much like intracellular pyruvate elevation, contributes to a vicious cycle that sustains elevated HIF-1 activity, as previously suggested by Vissers and colleagues [46].

Whether down-regulation of SVCT2 expression is a common motif in aggressive cancers, remains to be established by further research. Nonetheless, to the extent that such down-regulation is feasible, it would be reasonable to anticipate that cells experiencing such down-regulations would be enriched in invasive or metastatic lesions, whose capacities to spread are often reflective of up-regulated HIF-1 activity. And even if such down-regulation proves to be uncommon, a moderate decrease of the SCTV2 activity of acidic tumors can be anticipated.

It should also be noted the increased oxidant production characteristic of many aggressive cancers could be expected to lower intracellular ascorbate levels somewhat, independent of any alteration in SVCT2 activity, as ascorbate would be oxidized while quenching free radicals [16].

Two practical strategies for boosting the intracellular ascorbate levels of cancers in vivo can be envisioned: normalization of extracellular tumor pH via sodium bicarbonate administration; and intravenous infusion of dehydroascorbic acid.

Sodium bicarbonate therapy may boost SVCT2 activity in tumors

Gillies and colleagues, as well as other researchers, have shown that exposure to extracellular acidity in vitro enhances the invasive and angiogenic capacity of cancer cells, and makes them more prone to establish metastases when implanted or injected into rodents [51–57]. It is not clear to what extent modulation of intracellular ascorbate levels contributed to these results, since cell culture media are sometimes quite low in ascorbate; however, to the extent that ascorbate was present in the culture media, its uptake by the tumor cells presumably would have been relatively impaired at low pH. Activation of NF-kappaB and of AP-1 transcription factors appears to contribute to the pro-metastatic impact of mild acidity on some cancer cell lines [52,53]. In any case, Gillies and colleagues have shown that oral administration of well-tolerated quantities of sodium bicarbonate in water tends to normalize the extracellular pH of tumors, while not notably influencing plasma pH [58,59]. Moreover, they have reported that, in nude mice implanted with a human breast cancer, oral administration of sodium bicarbonate markedly suppresses the number and size of metastases formed in lung, visceral organs, and lymph nodes, while not influencing expansion of the primary tumor [60]. A few anecdotal reports of improved cancer control in cancer patients taking oral sodium bicarbonate have also appeared, and a formal clinical study evaluating this safe and incredibly cheap option in late-stage cancer patients is now underway.

In addition to rendering cancer cells more prone to invade and metastasize, extracellular acidity has the potential to lessen cancer chemosensitivity to mildly alkaline cancer drugs (which owing to protonation in the acidic tumor environment will have poor intracellular penetrance), and to suppress the activity of cytotoxic T lymphocytes and natural killer cells targeting the tumor [58,59,61–65]. So it will not be surprising if sodium bicarbonate administration proves to be a very worthwhile adjuvant measure for cancer management. And, to the extent that it does indeed succeed in elevating depressed tumor pH, it can be expected to boost ascorbate transport into tumor cells, thereby suppressing the HIF-1 activity of those cancers in which intracellular ascorbate levels are suboptimal to maximize HIF-1 hydroxylase activities.

Infusion of dehydroascorbic acid as an anticancer measure

Alternatively or additionally, intracellular ascorbate levels could be boosted – potentially quite substantially – by intravenous administration of dehydroascorbic acid (DHA – not to be confused with fish oil!) SVCT1/2 do not transport this molecule, but it can enter cells quite efficiently via various glucose transporters; GLUT-1 is particularly effective in this regard, and moreover tends to be highly expressed in cells with high HIF-1 activity, as this activity promotes GLUT-1 synthesis [42,66]. This transport is a facilitated diffusion, but, once inside cells, DHA tends to be rapidly reduced to ascorbic acid, which effectively is trapped in the cell (at least until it is reoxidized and metabolized, or extruded by certain low capacity mechanisms). The fact that DHA is reduced to ascorbic acid within cells is no mere happenstance. The oxidation of ascorbate during normal cellular metabolism results in the evolution of DHA; rapid reduction of this DHA back to ascorbate is a key reason why ascorbate can function so efficiently as an intracellular antioxidant. Hence, parenteral administration of DHA can readily increase the intracellular ascorbate content of cells to supraphysi-

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ological levels, and this phenomenon is particularly marked for aggressive cancer cells with elevated HIF-1 activity, in which GLUT-1 expression tends to be high [67,68]. Moreover, there is evidence that, even in the absence of DHA infusion, some cancers can employ this mechanism to increase their intracellular ascorbate content; oxidants produced in the microenvironment of cancer cells, of autocrine or paracrine origin, can generate some DHA from ascorbate in the extracellular space, which then can diffuse into the cells via GLUT transporters [69,70].

The fact that parenteral DHA administration can be used to achieve supraphysiological intracellular concentrations of ascorbate, has motivated studies evaluating DHA pre-administration on ischemia–reperfusion injury in rodents. Indeed, this strategy was found to confer marked protection in models of ischemia–reperfusion injury to the brain and liver [71,72].

Only a few published studies have examined the impact of DHA on cancer cells in culture or implanted in rodents – yet several of these studies report dramatic results. The first such traceable study, published in 1958 by German researchers, reported that DHA dose-dependently suppressed cancer cell glycolysis under both aerobic and anaerobic circumstances [73]. This finding is of course consistent with an expected suppression of HIF-1 activity – albeit this interpretation is sustained only if the anaerobic conditions were not completely anoxic. (Ascorbate could not be expected to support hydroxylase activities in the literal absence of oxygen). Moreover, these researchers also assessed the impact of intravenous DHA administration on various transplanted tumors in rats. In rats transplanted subcutaneously with Jensen sarcoma or Walker carcinoma, rapid tumor growth necessitated sacrifice of the animals after 15 days. In contrast, in rats given 2 mg/kg DHA intravenously on the same day as tumor transplantation, the tumors grew slowly until at 6–7 days they were the size of a cherry pit; the tumors then tended to regress, and all but one appeared to be completely resorbed; the one that remained palpable appeared extremely necrotic on autopsy. If the DHA infusion was postponed until 5 days after transplantation, tumor growth was very notably slowed, but no tumors were completely resorbed. Surprisingly, results with a much higher dose of DHA – 200 mg/kg – were not so notably impressive, though tumor growth was markedly slower than in the controls. These researchers also reported that the rats could tolerate single dose infusions of 350–500 mg/kg DHA, albeit some transitory dyspnea was noted.

This remarkable report by Heise and collegues appears to have been completely ignored, even by the other research groups that later documented an antitumor effect of DHA (they did not cite Heise's work). Conceivably, the fact that Heise saw his best results with such a low dose of DHA rendered his results incredible to scientists who presumed that DHA was functioning as a cytotoxic agent. But his results make perfect sense if the DHA is viewed as an agent for achieving high physiological ascorbate levels sufficient to optimize HIF-1 hydroxylase activities. Indeed, the very high intracellular ascorbate levels achieved with high-dose DHA conceivably could exert a countervailing pro-oxidant effect.

In research published in 1971, Japanese researchers examined the impact of DHA – injected subcutaneously at 150 mg/kg, every other day after tumor transplantion, commencing 30 h after transplantation [74]. The animals were autopsied and the tumors weighed after two weeks. Average tumor size in the treated group was 88% lower than that in the control group.

During the 1980s, Poydock and colleagues reported a series of studies in which DHA, administered alone or in conjunction with vitamin B12 or cobalt salts, was shown to prolong survival and retard tumor growth in mice implanted with Ehrlich carcinoma or P388 leukemia [75–77]. These studies employed the rather high DHA dose of 400 mg/kg for 8 consecutive days. The results of Poydock's studies have been lucidly summarized in a recent review by Toohey, who argues that the DHA alone was responsible for the observed benefits [78]. Toohey also makes the intriguing suggestion that DHA may have been selectively toxic to cancer cells because such cells tend to make homocysteine lactone, which can react with DHA to produce the potent toxin 3-mercaptopropionaldehyde.

It is certainly conceivable that, at relatively high parenteral doses, DHA could exert cytotoxic effects that are somewhat selective for cancer cells. Preferential uptake of DHA by cancers overpressing GLUT-1, or perhaps a peculiarity of cancer metabolism such as that highlighted by Toohey, might account for such selectivity. These intriguing reports merit confirmation and extension by other workers; the fact that they have been marginalized and neglected may in part be attributable to the fact that DHA is a natural metabolite for which pharmaceutical companies could not obtain a structure patent. Also, DHA is currently much more expensive than ascorbic acid, which could discourage research with this agent.

But the most intriguing report is clearly that of Heise and collegues, who reported marked response to low, quasi-nutritional doses of DHA. These results quite conceivably could reflect the impact of down-regulation of HIF-1 activity in aggressive cancer cell lines which have evolved dependency on this transcription factor. Indeed, the modest slow growth followed by stasis and resorption, reported for tumors treated with low-dose DHA, might be expected in cancers whose angiogenic or invasive capacity had been notably suppressed.

These considerations suggest that two types of studies with DHA would be worthwhile. First, cell culture studies could be employed to determine whether, in some cancer cell lines that continue to express meaningful HIF-1 under aerobic or mildly hypoxic conditions even when exposed to ascorbate in physiological serum concentrations, the addition of moderate concentrations of DHA can down-regulate HIF-1alpha levels or HIF-1 transcriptional activity. If such studies yield a positive outcome, then the impact of parenteral DHA administration on the growth and spread of such cancer cells in mice could be assessed. Responsive cancers would likely have down-regulated SVCT2 expression, an increased production of oxidants, and dependence on HIF-1 activity for their aggressive behavior; some cancers of many histologies, especially as they progress, would seem likely to meet these criteria.

Adjunctive strategies for controlling HIF-1 activity

Whereas boosting the intracellular ascorbate concentration of tumor cells may be the most direct way to protect HIF-1 hydroxylases from inhibition by oxidative stress, alternative strategies might also prove worthwhile in this regard. Since glutathione can mimic the protective impact of ascorbate in this regard to some degree, administration of adequate doses of N-acetylcysteine and phase two inducer compounds (lipoic acid or sulforaphane, for example) could potentially be of some value for controlling HIF-1 [17,79]. Preliminary evidence indicates that the chief phytochemical in spirulina, phycocyanobilin, may have the capacity to inhibit certain NADPH oxidase complexes, mimicking the physiological role of bilirubin this regard; hence, this agent may have potential for suppressing oxidant production in cancers that overexpress NADPH oxidase [21,80]. And it would be of interest to determine whether astaxanthin, a very potent membrane antioxidant, also of algal origin, could diminish to some extent the superoxide production of chronically hypoxic mitochondria – inasmuch as astaxanthin appears to have excellent potential as a mitochondrial antioxidant and has been markedly effective in animal models of ischemia–reperfusion damage [81–86]. With respect to pyruvate's impact on HIF-1 activity, the drug dichloroacetate inhibits pyruvate dehydrogenase kinase-1,

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and hence has the potential to rectify the elevation of pyruvate levels seen in cancer cells expressing the Warburg phenomenon [87–89].

As noted above, up-regulation of HIF-1alpha expression at the transcriptional and translational levels, as well as a MAP kinase-catalyzed phosphorylation that promotes its nuclear localization, can contribute to elevated HIF-1 activity in many cancers. Potentially practical clinical strategies for addressing these issues have been summarized in a previous communication [6].

Overview

In summary, there is reason to suspect that in some aggressive cancers that experience increased oxidative stress (owing to increased oxidant production and/or diminished catalase activity) and/or have elevated levels of pyruvate, intracellular levels of ascorbate may be too low to maintain optimal activities of HIF-1 hydroxylases, even when serum ascorbate concentrations are high-normal. This relative deficit of ascorbate might often reflect diminished expression or activity of SVCT2, though increased oxidative stress would itself tend to diminish ascorbate levels. Regular oral administration of sodium bicarbonate, by normalizing extracellular tumor pH, could be expected to boost the transport activity of SVCT2 in many tumors. And intravenous administration of moderate doses of DHA, repeated at some appropriate interval, could be expected to achieve and maintain notable elevations of cancer cell ascorbate content. These concepts could be assessed in cell culture studies, rodent studies, and – if the preceding studies have proved fruitful – clinical trials. These strategies might prove most fruitful in the context of anti-angiogenic therapies which, even when they initially achieve tumor regression or stasis, typically fail to markedly increase survival owing to selection for aggressive variants in which HIF-1 is highly active [1,6].

As a proviso, it should be noted that DHA loading of cancer may be contraindicated in the context of certain cytotoxic chemotherapies whose killing mechanism requires induction of oxidative stress. For example, Heaney and colleagues showed that pre-loading a human lymphoma implanted in nude mice with DHA subsequently blunted the ability of doxorubicin to control its growth; these researchers further showed that DHA pre-loading protected cancer cell lines from a range of cytotoxic agents in vitro [67]. Ironically, this contraindication might extend to use of high-dose intravenous sodium ascorbate in cancer therapy; this kills certain cancers by generating hydrogen peroxide within the tumor [90–92]. Conversely, high-dose intravenous sodium ascorbate may potentiate the cytotoxic efficacy of certain anti-cancer drugs [93,94]. Hence, a rational way to exploit vitamin C in cancer therapy would be to load cancer with DHA in intervals between chemotherapy, and to administer high-dose intravenous sodium ascorbate in conjunction with chemotherapy; optimal intracellular concentrations of ascorbate have the potential to slow cancer growth, whereas very high extracellular concentrations of ascorbate have the potential to kill certain cancers, and potentiate their response to cytotoxins. More generally, a strategy of maximizing oxidative stress on a cancer during cytotoxic therapy, and minimizing that oxidative stress in the intervals between such therapy, has logical merit [95].

Conflict of interest

None.

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