Lactate: A Metabolic Key Player in Cancer

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Abstract

Increased glucose uptake and accumulation of lactate, even under normoxic conditions (i.e., aerobic glycolysis or the Warburg Effect), is a common feature of cancer cells. This phenomenon clearly indicates that lactate is not a surrogate of tumor hypoxia. Tumor lactate can predict for metastases and overall survival of patients, as shown by several studies of different entities. Metastasis of tumors is promoted by lactate-induced secretion of hyaluronan by tumor-associated fibroblasts that create a milieu favorable for migration. Lactate itself has been found to induce the migration of cells and cell clusters. Furthermore, lactate bridges the gap between high lactate levels in wound healing, chronic inflammation, and cancer development. Lactate is a key player in the determination of extracellular matrix components, immune escape, and angiogenesis. Furthermore, lactate itself has been found to induce the migration of cells and cell clusters. In summary, accumulation of lactate in solid tumors is a pivotal and early event in the development of malignancies. The determination of lactate in solid tumors is a pivotal and early event in the development of malignancies. The determination of lactate in solid tumors is a pivotal and early event in the development of malignancies. The determination of lactate in solid tumors is a pivotal and early event in the development of malignancies. The determination of lactate in solid tumors is a pivotal and early event in the development of malignancies. The determination of lactate in solid tumors is a pivotal and early event in the development of malignancies. The determination of lactate in solid tumors is a pivotal and early event in the development of malignancies. The determination of lactate in solid tumors is a pivotal and early event in the development of malignancies. The determination of lactate in solid tumors is a pivotal and early event in the development of malignancies. 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Consequently, and consistent with Warburg's (1) observations, expression of HIF-1–regulated genes leads to an enhanced flux of glycolysis in tumor cells in an oxygen-independent manner. Thus, the phenomenon of lactate accumulation in solid tumors is not just a surrogate of hypoxia (6). Yaromina and colleagues (7) showed that on the microregional level, high lactate concentrations were not associated with hypoxia. (The relevance of hypoxia in terms of glucose metabolism is reviewed elsewhere in the literature and is not the main topic of this article.) The targets of HIF-1 include membrane transporters, such as glucose transporter 1 (GLUT-1) and monocarboxylate transporter 4 (MCT-4), that ensure both adequate glucose delivery into the cell and secretion of accumulated lactate out of the cell. Furthermore, due to enhanced lactate dehydrogenase A (LDH-A) expression, NAD⁺ is generated, permitting continued glycolysis and ATP production. HIF-1–dependent activation of pyruvate dehydrogenase kinase 1 and the resulting inactivation of the pyruvate dehydrogenase complex contribute to decreased flux in oxidative phosphorylation. Despite the high conversion rate of pyruvate into lactate at the end of the glycolytic pathway, some pyruvate remains to be used in the tricarboxylic acid (TCA) cycle for bioenergetic and biosynthetic purposes (4). The TCA cycle and the pentose phosphate pathway (PPP) can maintain a high precursor pool to maximize tumor cell proliferation at the expense of the surrounding normal tissue or the host in general. In addition, PPP generates NADPH as a mediator of antioxidative reactions to protect cells from oxidative damage (3). Besides glycolysis, glutaminolysis is another main source for energy production and seems to contribute to elevated lactate accumulation in tumor cells. Glutaminolysis also enables synthesis of macromolecules in proliferating cells (4). Another source of lactate is provided by the tumor-specific isoform of pyruvate kinase (PK) M2, which converts phosphoenolpyruvate (PEP) into pyruvate. However, PEP can also serve as a phosphor donor for phosphoglycerate mutase 1 (PGAM1), leading to the formation of pyruvate independently of PKM2 activity (8). Overall, it seems to be a common feature of most other pivotal enzymes of the...
glycolytic pathway to switch to fetal-type isoforms of these enzymes to support the large-scale anabolic programs required for active proliferation (9).

Evidence from recent data suggests that a deregulation of glycolysis may be involved in epigenetic mechanisms of gene regulation in cancer cells. In particular, Buchakjian and Kornbluth (10) depicted the influence of pyruvate on histone acetylases (HAT) and histone deacetylases (HDAC) leading to an increase in transcription of glycolytic enzymes and transporters. As a consequence, metabolites of glycolysis may be involved in epigenetic feedback loops that are still poorly understood, necessitating further research efforts in this field.

Recent data suggest that the metabolic switch toward deregulation of glycolysis may be an early and fundamental event in tumorigenesis. Findings of Schafer and colleagues (11) showed that upregulation of glycolysis in detached Her2/neu + ductal breast cancer cells could provide them with a survival advantage by preventing the downregulation of EGF receptor and thus maintaining the activation of the PI3K pathway. Ong and colleagues (12) found an immense increase in glucose consumption in premalignant intestinal polyps, as well as in adenocarcinomas compared with nonmalignant mucosa. Some of the regulating molecules of neoplastic transformation, such as NF-κB, are involved in the coordination of inflammation. This yields a link to the earlier view of cancer as an "overhealing wound" (13). Furthermore, most of the genes that orchestrate the wound-healing process are also important positive or negative regulators of cancer growth and progression (13). Lactate itself functions as an intrinsic inflammatory mediator that leads to increased interleukin (IL)-17A production by T cells and macrophages, resulting in the promotion of chronic inflammation in tumor microenvironments (14).

Contribution of Lactate to Immune Escape

One major reason for tumor development is the inability of the immune system to adequately eliminate aberrant cells. Intense recent research efforts have elaborated several escape mechanisms of tumor cells, including upregulation of inhibitory molecules, production of immunosuppressive cytokines, and downregulation of costimulatory molecules (15). Besides these mechanisms, tumor metabolism largely contributes to the immunologic escape. Recently, extracellular lactate was found to inhibit the differentiation of monocytes to dendritic cells (DC) and to inactivate the cytokine release from DCs (16) and cytotoxic T cells (17), the key player in antitumoral response.

Immunohistologic analyses of tumors indicate a high number of tumor-infiltrating lymphocytes, which suggests that the missing immune response is not mainly a failure of recognition mediated by a downregulation of MHC-I together with tumor-associated antigens but, rather, a functional impairment of the adaptive immune system on the effector side. Activated T cells themselves use glycolysis as their main energy source (17). When the tumor cells release high amounts of lactate to the extracellular space, the immune cells cannot rid themselves of their own lactate, because cellular lactate secretion is dependent on the ratio of intra- to extracellular concentration. Ultimately, leukocytes may be asphyxiated by lactate. Because cellular lactate secretion via MCTs is accompanied by H+ transport, a decrease in extracellular pH results in a reduction of cytotoxic T-cell function (17, 18). In contrast, regulatory T cells (Treg) do not appear to be affected by the presence of lactate and an acidic microenvironment, because they have a different energy metabolism that relies on fatty acid oxidation (19). This could explain why the overall immune cell infiltration rate in solid tumors does not predict for either outcome of disease or patient survival.

Differential Influence of Lactate on Cell Migration

In classic Boyden chamber experiments, the addition of exogenous lactate led to a concentration-dependent increase in random migration of various cancer cell lines (20). This was true for lactate levels that are relevant for solid tumors in vivo (i.e., 0–40 mmol/L). Furthermore, the lactate-mediated enhancement of tumor cell motility was seen not only in single-cell motion but also in enforced bulk migration by means of time-lapse videomicroscopy (20). Although lactate-induced changes in signal protein levels and their activation status, such as β1-integrins, have been registered, the molecular mechanisms involved in the impact of lactate on cell motility are still not understood. Recent data support the TGF-β2 signaling pathway as being a mediator of the lactate-associated effects on migration of cancer cells (21).

Employing the same experimental setup as that used for cancer cells, Goetz and colleagues (20) showed that exogenous lactate invariably inhibited the migration of monocytes. This finding was paralleled by a concentration-dependent reduction of cytokine release, such as that of IL-6 or TNF-α. It should be pointed out here that pH was clamped at 7.2 under ambient oxygen supply throughout these experiments.

Boyden chamber experiments showed that lactate stimulates VEGF production by endothelial cells (EC), leading to enhanced migration and resulting in lactate-induced angiogenesis independently of O2 conditions (22). Recently, Végrán and colleagues (23) published an article in this journal in which they stated that lactate uptake in ECs through MCT-1 stimulates NF-κB activity and IL-8 expression. With the use of mouse xenograft models, they showed that lactate release from tumor cells through MCT-4 is sufficient to stimulate IL-8-dependent angiogenesis and tumor growth.

Lactate added to cultured fibroblasts increases their hyaluronan production and leads to elevated expression of CD44, a transmembrane glycoprotein and the predominant hyaluronan receptor on cell surfaces. The stroma that surrounds carcinomas has increased hyaluronan produced by tumor-associated fibroblasts (TAF), providing an environment that promotes the growth and motility of cancer cells (24, 25).

Clinical Relevance of Lactate Accumulation in Primary Tumors

In 2000, data from our laboratory was published in this journal showing that lactate accumulation in primary cervical
cancer was inversely correlated with patient survival, as sur-
veyed in a follow-up period of up to 9 years (26). To our
knowledge, this was the first sound demonstration in a clinical
setting that tumor lactate metabolism is closely linked to
the aggressiveness of cancer. We acquired the data on meta-
bolite concentrations in tumor tissue using the natural
specific enzyme LDH as a sensor of lactate. This enzyme is
biochemically linked to luciferase in such a way that the
intensity of the emitted bioluminescence is proportional to
the metabolite concentration. Using appropriate standards,
one can calibrate the light signal in units of tissue concentra-
tion, such as micromoles per gram of tissue (µmol/g). The
bioluminescence reaction can be induced in cryosections from
snap-frozen tissue, which makes it possible to register the light
signal in relation to the histologic structure of the tissue.
In essence, induced metabolic bioluminescence imaging
(imBI) allows for quantitative and structure-associated detec-
tion of metabolites in tissues ex vivo with a resolution on the
microscopic level. Because of these unique traits, the appli-
cation of imBI in animals and humans resulted in novel
information for basic and translational cancer research, as
outlined below.

Shortly after publication of the above-mentioned data on
lactate in primary cervical cancer and its correlation to patient
survival, an independent study on patients with head and neck
squamous cell carcinoma (HNSCC) also showed that prether-
apeutic lactate concentrations of individual primary tumors
were inversely correlated with overall and disease-free patient
survival, predominantly after combined radiochemotherapy
(25, 27). Furthermore, the lactate content of tumors from all
entities investigated revealed a significant positive correlation
with the incidence of (distant) metastases (25). Lactate con-
centrations within tumors of the same stage and grade were
found to be largely variable in these studies. In the 3 entities
analyzed, lactate concentrations in viable tumor regions
showed tremendously large intra- and intertumoral variations
compared with other metabolites, such as ATP and glucose.
Nevertheless, intratumoral lactate variations were much small-
er than intertumoral differences. The findings on the clinical
relevance of lactate accumulation in tumors were obtained
with the imBI technique. At present, no noninvasive technique
is available that offers a comparable combination of advan-
tages. Also, it is still not clear which classes of lactate (i.e.,
unbound vs. bound to protein vs. total lactate) can be detected
with the various invasive and noninvasive approaches. How-
ever, some recent noninvasive studies have concentrated on
lactate quantification and its potential clinical relevance. In
studies similar to our own, Saraswathy and colleagues (28)
showed that higher lactate intensities from proton magnetic
resonance spectroscopic imaging measurements were associ-
ated with poor survival in patients with glioblastoma multi-
forme. Park and colleagues (29) showed significantly higher 13C
lactate levels in human glioblastoma xenografts compared
with normal rat brains. Other studies used 13C spectroscopy
or high-resolution magic-angle spinning (30).

Application of quantitative imaging techniques for lactate
before and during treatment by targeting metabolism could
provide valuable information about target specificity, tumor
response, and clinical outcome. This is probably the most
important role for lactate measurements in the current clinical
research and practice environment.

Contribution of Lactate to Radioresistance

Results from a study group (including our laboratory) on
experimental tumors, including more than 1,000 individual
xenografts of human HNSCC, showed that lactate concen-
trations are positively correlated with radioresistance (31).
This correlation could be due, at least in part, to the
antioxidant properties of lactate as revealed in a previous
study (32). Anticancer therapies, such as ionizing radiation
and several chemotherapeutic drugs, induce oxidative stress
in targeted cells. Overproduction of reactive oxygen species
(ROS) leads to DNA and RNA damage, lipid peroxidation,
and genomic instability. ROS are required for the fixation
of radiation-induced DNA damages; therefore, an accumula-
tion of antioxidants (e.g., lactate) may induce or enhance
resistance to radiation and may cause chemoresistance (33).
Because lactate has been shown to decrease after che-
otherapy or radiotherapy in animals (34), monitoring this
metabolite in human tumors may allow for the prediction of
therapeutic responses.

In conclusion, manipulation of glycolysis to alter the levels
of antioxidant metabolites, and therefore ROS quantities, may
lead to a better therapeutic response.

Conclusions and Future Prospects

Tumor cells perform a metabolic switch to produce inter-
mediates for increased cell growth and division. This appears
to be a very early (if not the initial) event in carcinogenesis, at
least in a significant number of cases observed so far. On the
basis of our current knowledge, it is too early to draw firm
conclusions about a causative role of deregulated glycolysis in
tumorigenesis. However, an increasing amount of data
support the use of such an assumption as a working hypothesis
for future basic research on tumor metabolism. Trying to
elucidate the "hen and egg problem" in the sequence of
inflammatory events, metabolic deregulation, genetic altera-
tions, and acquisition of functional malignancy represents an
exciting challenge in experimental cancer research.

Although several genetic, biochemical, and pathophysio-
logic mechanisms have been identified as causes of the high
degree of malignancy in high-lactate tumors, it remains
obscure why seemingly identical tumors may exhibit extreme
differences in their tissue content of lactate. This is certainly
another challenge for future research in this field.

Despite this missing knowledge, translational research on
tumor metabolism has moved on to transfer some basic
aspects of cancer research to the clinical setting. Tennant and
colleagues (35) compiled an impressive number of trials in
clinical oncology up to phase III based on manipulating tumor
metabolism. All researchers working in this field are encour-
aged to make their contribution to the common effort of
utilizing tumor metabolism for the diagnosis and treatment
of cancer.
Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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