

Lactate: A Metabolic Key Player in Cancer

Franziska Hirschhaeuser, Ulrike G.A. Sattler, and Wolfgang Mueller-Klieser

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, radioresistance has been positively correlated with lactate concentrations, suggesting an antioxidative capacity of lactate. Findings on interactions of tumor metabolites with immune cells indicate a contribution of lactate to the immune escape. Furthermore, lactate bridges the gap between high lactate levels in wound healing, chronic inflammation, and cancer development. Tumor cells ensure sufficient oxygen and nutrient supply for proliferation through lactate-induced secretion of VEGF, resulting in the formation of new vessels. In summary, accumulation of lactate in solid tumors is a pivotal and early event in the development of malignancies. The determination of lactate should enter further clinical trials to confirm its relevance in cancer biology. *Cancer Res*; 71(22); 6921–5. ©2011 AACR.

Introduction

Warburg's pioneering studies in the 1920s and his published findings (1) were followed by tremendous amounts of research in the field of tumor glycolysis and lactate metabolism. For many years, the majority of these studies were focused on the biochemical regulation of carbohydrate metabolism in isolated tumor cells and tumor cell lines. At the same time, radiotherapy of tumors was continuously advanced and became increasingly efficient with seemingly one major limitation: A restricted oxygen supply and an imbalance between oxygen supply and consumption cause hypoxia in many tumors. As a consequence, investigations on hypoxia, including its causes and consequences for the cancer patient and its susceptibility to therapeutic manipulation, dominated research on tumor metabolism and microenvironment for many years. In contrast to tumor hypoxia, tumor glycolysis and lactate biology received little scientific attention for many years. However, findings concerning overexpression of glycolysis-related genes in 70% of all human cancers worldwide (2) and the exploitation of increased glucose uptake of cancer cells for tumor diagnosis-

tics by positron emission tomography with ^{18}F -fluorodeoxyglucose contributed to the topic once again experiencing a renaissance. This may lead to improvement of cancer diagnosis and therapeutic follow-up in a clinical setting, as reviewed in this article. Our view of lactate as a key player in tumor metabolism is illustrated in Fig. 1.

Metabolic Switch in Tumorigenesis

Malignant transformation of normal cells leads to increased glucose uptake and lactate formation even under normoxic conditions in most solid tumors. It is commonly accepted that this phenomenon is a consequence of defects in cellular respiration, oncogenic alterations, and overexpression of glycolytic enzymes and metabolite transporters (3). A number of oncogenes and tumor suppressor genes are involved in the metabolic switch from oxidative phosphorylation (OXPHOS) toward an altered glycolysis of tumor cells, such as *myc*, *NF- κ B*, Akt/protein kinase B, epidermal growth factor (EGF), insulin-like growth factor I, phosphoinositol 3 kinase (*PI3K*), mTOR, Kirsten rat sarcoma viral oncogene homolog (KRAS), AMP-activated protein kinase (AMPK), and hypoxia-inducible factor 1 α (*HIF-1 α* ; refs. 3 and 4). Most of these oncogenes have been shown to stimulate genes encoding for proteins that mediate glycolysis and glutaminolysis. A key player in cellular adaptation is the transcription factor HIF-1 α , which is usually controlled by cellular oxygen concentrations via prolyl hydroxylases and the von Hippel-Lindau complex. Note that HIF-1 α is stabilized even under normoxic conditions by the products of glycolysis, lactate and pyruvate, which leads to an accumulation of this master transcription factor (5).

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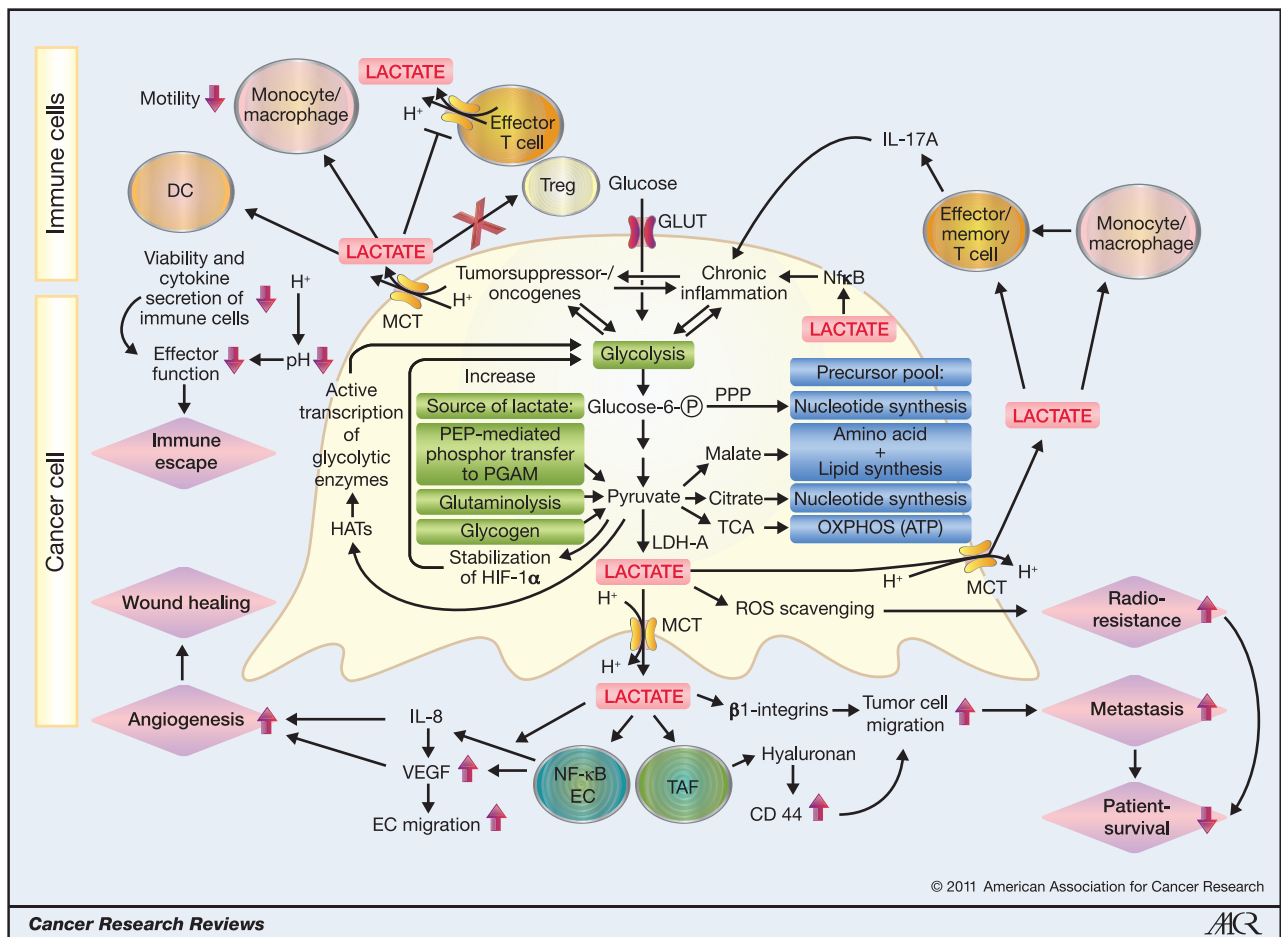


Figure 1. Illustration of lactate as a key player in cancer. DC, dendritic cell; EC, endothelial cell; GLUT, glucose transporter; IL, interleukin; HAT, histone acetylase; LDH, lactate dehydrogenase; MCT, monocarboxylate transporter; PEP, phosphoenolpyruvate; PGAM, phosphoglycerate mutase; PPP, pentose phosphate pathway; ROS, reactive oxygen species; TAF, tumor-associated fibroblast.

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- κ B, 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 depen-

dent 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 (T_{reg}) 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 signaling protein levels and their activation status, such as β 1-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- β 2 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, Goetze and colleagues (20) showed that exogenous lactate invariantly 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, Végran and colleagues (23) published an article in this journal in which they stated that lactate uptake in ECs through MCT-1 stimulates NF- κ B 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 surveyed 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 metabolite 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 concentration, such as micromoles per gram of tissue ($\mu\text{mol/g}$). 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 detection of metabolites in tissues *ex vivo* with a resolution on the microscopic level. Because of these unique traits, the application 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 pretherapeutic 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 concentrations 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 smaller 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 advantages. 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. However, 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 associated with poor survival in patients with glioblastoma multiforme. Park and colleagues (29) showed significantly higher ^{13}C lactate levels in human glioblastoma xenografts compared with normal rat brains. Other studies used ^{13}C 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 concentrations 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 accumulation 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 chemotherapy 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 intermediates 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 alterations, and acquisition of functional malignancy represents an exciting challenge in experimental cancer research.

Although several genetic, biochemical, and pathophysiologic 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 encouraged 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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