Lactic Acid: No Longer an Inert and End-Product of Glycolysis

For decades, lactic acid has been considered a dead-end product of glycolysis. Research in the last 20+ years has shown otherwise. Through its transporters (MCTs) and receptor (GPR81), lactic acid plays a key role in multiple cellular processes, including energy regulation, immune tolerance, memory formation, wound healing, ischemic tissue injury, and cancer growth and metastasis. We summarize key findings of lactic acid signaling, functions, and many remaining questions.

The chronology of lactic acid (L-lactic acid) began in 1808 when Berzelius, a Swedish chemist, first described the accumulation of lactate in living animals (in the muscle of stags) (86). Almost 100 years later, it was recognized that lactic acid is a type of energy donor for muscle contraction (139). In the late 1920s, ATP was discovered (42), and finally, in the 1940s, the entire glycolytic (Enbden-Meyerhof) pathway was elucidated (81). For the next 40+ years, lactic acid was considered an inert product of glycolysis during hypoxia (145). However, evidence accumulated in the last almost three decades has shown otherwise. Depending on the circumstances, lactic acid can be fuel donor or can exert multiple regulatory functions in many physiological and pathological conditions. Here, we highlight some important findings in the areas of lactic acid transport, signaling, and functions in several pathophysiological processes.

Lactic Acid Homeostasis

In an average adult, ~1,500 mM of lactic acid enters circulation daily from muscle (25%), skin (25%), brain (25%), red blood cells (20%), and intestine (10%). The lactic acid [pKₐ 3.86, >99% dissociates to lactate and proton (H⁺) at pH of 7.35–7.45 (54)] is cleared predominantly by the liver via gluconeogenesis (Cori cycle) and ATP production (oxidative phosphorylation, Krebs cycle) (Table 1). The hepatic uptake of lactate can increase by >10-fold during exercise (1, 2, 18). Cardiac myocytes also take up and oxidize lactate as fuel (149, 150). Lactate contributes to the cardiac energy provision by ~10–15% at rest (52, 106) and ~30% during moderate-intensity exercise (52). In rodents, deprivation of circulating lactate impairs myocardial function (87). In the kidney, there is a smaller amount of lactic acid production in the medulla and utilization in the cortex (80). Lactate as a glucose-precursor can account for >50% of gluconeogenesis in the kidneys. The contribution of glucose appearance in circulation by kidney gluconeogenesis can increase substantially from ~5–16% to 40% during fasting, hypoglycemia, increased circulating adrenaline, and exercise (102). In the brain, glycolysis is prominent, accounting for 10–12% of glucose consumption (56). Circulating lactic acid can accumulate in a number of pathological conditions, also known as lactic acidosis. In critically ill patients, lactic acidosis portends poor prognosis and high mortality (80).

Lactic Acid (H⁺ and Lactate Anion) Transport and Signaling

Monocarboxylate Transporters

Lactic acid is transported across the plasma membrane by several monocarboxylate transporters (MCTs) that belong to the SLC16 gene family. To date, 14 MCTs have been identified (59, 61, 74). The MCTs are membrane proteins with 12 transmembrane domains, intracellular NH₂ and COOH termini, and a large cytosolic loop between transmembrane domains 6 and 7. Of the 14, MCTs 1–4 (encoded by SLC16A1, SLC16A7, SLC16A8, and SLC16A3, respectively [60]) are better characterized. Two MCT ancillary proteins, embigen (gp70) and basigin (also known as CD147 or EMMPRIN or HT7 or OX-47), have been identified. Basigin is crucial for MCT1, 3, and 4 expression, plasma membrane trafficking, and their acid shuttling activity (13, 79, 148). Embigen is critical for proper plasma membrane expression of MCT2 (107). CD44 has been shown to be associated with MCT1/MCT4/CD147 complex and may potentially be another MCT ancillary protein (8).

MCTs 1–4 have been shown to facilitate the transmembrane H⁺-linked transport of monocarboxylates, including lactate, pyruvate, acetocetate, and β-hydroxybutyrate (29, 32, 61, 89, 116). The driving force for the transport includes the trans-membrane substrate concentration gradient and local H⁺ availability. Carbonic anhydrase 9 has...
be shown to interact with MCT1 and to shuttle H\(^+\) through its “H\(^+\)-distributing antenna” for MCT1-mediated lactic acid flux (73). MCT1 is ubiquitously expressed in humans (41, 113). It shows an intermediate affinity for its substrates (\(K_m\) lactate = 3.5–10 mM) and is involved in both uptake and extrusion of monocarboxylates from cells. Three-dimensional molecular structure of MCT1 in both cytosolic-substrate binding (closed) and extracellular-substrate binding (open) conformations have been described in detail (99, 147). An uptake cycle involves sequential steps in which H\(^+\) binds before the lactate anion, followed by a domain rearrangement during which lactate and H\(^+\) pass through the channel between the extracellular and intracellular binding sites, and released lactate first and H\(^+\) second. MCT1 can carry out up to 12 cycles/s (147). MCT2 has a high affinity to its substrates (\(K_m\) lactate = 0.5 mM). It has a more restricted tissue distribution (89), mostly in tissues that utilize lactate as fuel, such as brain (41, 111), heart, kidney, liver, and red skeletal muscles (41, 47, 59, 75). MCT2 functions primarily to import monocarboxylates (14, 89). MCT3 is comparatively less studied. It has an intermediate substrate affinity (\(K_m\) lactate = 6.0 mM in one study (58)). MCT4 shows a low affinity to its substrates (\(K_m\) lactate = 22 mM) and is expressed in highly glycolytic tissues, such as white skeletal muscle, astrocytes, and white blood cells (32, 113, 146). It functions mainly to export lactic acid (61, 146).

**Lactate Receptor GPR81**

Lactate can act as a ligand for GPR81 (also known as hydroxy-carboxylic acid receptor 1 (HCAR1)), a \(G_i\)-protein-coupled receptor. GPR81 activation down-regulates cAMP and attenuates protein kinase A (PKA)-mediated signaling (83). In addition, recent studies have shown that, in certain settings, lactate-induced GPR81 activation can signal through a noncanonical, cAMP/PKA-independent pathway involving β-arrestin, a GPR81 adaptor protein (38, 65).

GPR81 is expressed predominantly in the adipose tissue (16). It is also expressed, to a lesser degree, in a wide range of tissues and organs, including skeletal muscle (51, 82), liver, kidney, and brain (85). GPR81 has an estimated molecular mass of 40 kDa. It contains seven transmembrane domains, extracellular NH\(_2\) and intracellular COOH termini, and three extracellular and three cytosolic loops. Using site-directed mutation analyses, Kuei et al. show that Arg71 at the transmembrane domain 2, C165-E166-S167-F168 motif at the second extracellular loop, and highly conserved six Cys residues are critical for GPR81 function. In addition, computational modeling indicates that Arg71, Arg99, Glu166, and Arg240 of the human GPR81 molecule are involved in lactate binding (82).

Selectivity of GPR81 for lactate is within a wide range of 0.1–300 mM. EC\(_{50}\) for lactate has been reported to be −1–5 mM. The receptor can be partially activated at a lactate concentration of 0.2–1.0 mM (31). Thus physiological concentrations of lactate are sufficient to activate GPR81. In addition to lactate, the known ligands for GPR81 include 3,5-dihydroxybenzoic acid (3,5-DHBA; EC\(_{50}\): 0.15 mM) (90), 3 chloro-5-hydroxybenzoic acid (EC\(_{50}\): 0.02 mM) (35), and compound 2 (EC\(_{50}\): 50 mM) (121). Although predominantly distributed in the plasma membrane, GPR81 has recently been detected in the intracellular organelles, implying a role for GPR81 in the trafficking of lactate between the plasma membrane and intracellular compartments (91).

**Role of Lactic Acid in Several Biological and Pathophysiological Processes**

Mounting evidence indicates a role for glycolysis-derived lactic acid/lactate in the regulation of a

### Table 1. Simplified metabolic equations concerning lactic acid generation and metabolism in the cytosol

<table>
<thead>
<tr>
<th>Equation</th>
<th>Reaction</th>
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<td><strong>Equation 1</strong></td>
<td>(\text{C}_6\text{H}_12\text{O}_6 + 2\text{ADP}^{3-} + 2\text{Pi}^{2-} \rightarrow 2\text{CH}_3\text{CH(OH})\text{COO}^- + 2\text{ATP}^{4-} + 2\text{H}_2\text{O})</td>
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<tr>
<td><strong>Equation 2</strong></td>
<td>(2\text{ATP}^{4-} + 2\text{H}_2\text{O} \rightarrow 2\text{ADP}^{3-} + 2\text{Pi}^{2-} + \text{2H}^+)</td>
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<tr>
<td><strong>Equation 3</strong></td>
<td>(\text{LDH} \rightarrow \text{CH}_3\text{COOO}^+ + \text{NAD}^+ + \text{NADH} + \text{H}^+)</td>
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<tr>
<td><strong>Equation 4</strong></td>
<td>(2\text{CH}_3\text{CH(OH})\text{COO}^- + \text{2H}^+ \rightarrow \text{C}_6\text{H}_12\text{O}_6)</td>
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**Equation 1** shows simplified conversion of glucose to lactate. Two ATPs are generated. **Equation 2** shows that the two ATPs in Eq. 1 are promptly consumed, and 2H\(^+\) are released, causing acid build-up. **Equation 3** shows the reversible reaction between lactate and pyruvate catalyzed by the cytosolic enzyme lactate dehydrogenase (LDH). Lactate reacts with oxidized nicotinamide adenine dinucleotide (NAD\(^+\)) to form pyruvate, reduced nicotinamide adenine dinucleotide (NADH), and a proton (H\(^+\)). Under physiological condition, the concentration of lactate is ~10-fold that of pyruvate. Note that 1) the reaction is influenced by the ratio of NAD\(^+\) to NADH (redox state) and 2) LDH is stereo-specific and catalyzes conversion between L-lactate (not D-lactate) and pyruvate. **Equation 4** shows gluconeogenesis from lactate, which primarily takes place in the liver and, to a lesser degree, in the kidneys. 2H\(^+\) are utilized during the process. For each H\(^+\) utilized, equimolar OH\(^-\) (base) is generated. Thus lactate uptake by the liver is considered “converting” equimolar lactate to bicarbonate (base).
variety of pathophysiological processes. Several of these are discussed below.

**Energy Regulation**

The involvement of lactic acid/lactate in energy regulation has been extensively studied in adipose tissue, where insulin stimulates glucose uptake and lactic acid production under normoxic condition. Through MCTs, lactic acid exits the cell, and lactate, in an autocrine fashion, engages GPR81, which in turn downregulates adenyl cyclase activity, leading to a reduced cAMP generation (FIGURE 1). Since insulin receptor activation stimulates cAMP degradation (through activation of PI-3-K/AKT/phosphodiesterase), the dual processes of reduced generation and accelerated degradation of cAMP ensures a diminished cellular cAMP, resulting in a reduction of lipolysis (3), thus conserving energy-rich fatty tissue storage (15, 91).

In the exercising skeletal muscles, $P_O_2$ is reduced (to a semi-ischemic degree) due to consumption, and glycolysis increases. Accumulate of glycolysis-derived lactate elevates the cytosolic NADH-to-NAD$^+$ ratio (15, 158), which, together with an elevated ADP-to-ATP ratio, stimulates oxidative phosphorylation, ensuring ongoing energy supply (FIGURE 1). In this process, mitochondria behave as a sink for pyruvate and NADH, and lactate shuttling via MCTs is critical. In rodent skeletal muscle cells, lactate has been shown to stimulate mRNA of MCT1 and PGC-1α expression, promoting lactic acid shuttling as well as mitochondrial biogenesis (62, 88). These data are consistent with the observations that physical training renders more efficient lactate utilization by the muscles (11). The dual processes of glycolysis and oxidative phosphorylation work in concert to optimize muscle performance; lactic acid/lactate plays a key role in both processes.

In the brain, glycolysis has been shown to foster synaptic growth and remodeling (56). Depending on the regions of the brain, both glycolysis and oxidative phosphorylation operate cooperatively to augment the ratios of NADH/NAD$^+$ and ADP/ATP

**FIGURE 1.** Lactic acid, MCTs, and GPR81 form an autocrine loop, limiting lipolysis in the adipose tissue

Lactic acid, accompanied by NADH/NAD$^+$ and ADP/ATP in the exercising skeletal muscles, promotes sustained ATP generation through oxidative phosphorylation. Lactic acid also promotes wound healing, immune tolerance/anti-inflammation, and long-term memory formation in the brain (detailed in the text). Lactate also activates a yet-to-be fully defined noncanonical pathway through engaging GPR81.
(158), akin to the process in exercising skeletal muscles. Elevated NADH-to-NAD⁺ ratio also contributes to the regulation of cerebral blood flow (69, 103, 138). Gordon et al. show that elevated extracellular lactate inhibits regional prostaglandin (PGE2) uptake by the neurons and astrocytes, leading to prostaglandin accumulation and prostaglandin-mediated vasodilation. In addition, low oxygenation during neuronal activation facilitates ADP buildup and elevates extracellular adenosine. Adenosine, through activating its receptor ADAR2, prevents astrocyte-mediated vasoconstriction (55). GPR81 is widely expressed in the brain. Extracellular lactate, through activating GPR81 and cAMP reduction (85), can theoretically contribute to the regional vasodilation. This possibility, however, requires further investigation. Collectively, notwithstanding the fact that multiple signaling pathways (mediated by nitric oxide, glutamate, and epoxyeicosatrienoic) can all be contributory, evidence supports a role of lactate in the regulation of the cerebral vessel diameter and blood flow, and in contributing to the neuro-vascular coupling to meet the demands of neuronal activity. In line with these observations, cognitive function can be improved in the setting of hypoglycemia by lactate infusion (77, 78, 100, 137). These effects can also be affected by aging (39). As detailed below, glycolysis is also an important energy source and regulator in immune cells and immune responses. Overall, given the energy regulatory role of lactate in multiple tissues, this effect seems to be a general phenomenon.

**Anti-inflammation and Immune Tolerance**

In addition to being an important energy source for both innate and adaptive immune systems (19, 44, 46, 76), lactic acid generated from aerobic glycolysis (Warburg phenomenon) modulates inflammation and promotes immune tolerance. Studies have shown that lactic acid treatment of dendritic cells increases cellular production of anti-inflammatory interleukin-10 (IL-10) and diminishes the production of proinflammatory IL-12 in response to toll-like receptor (TLR) stimulators (105). Lactic acid also has been shown to downregulate TNF, NF-κB, and PTX-3, and to upregulate IL-23 in monocytes. Furthermore, lactic acid is capable of transiently downregulating chemokines, mediated by a delayed LPS-induced AKT phosphorylation and IκB degradation (110). Lactate can inhibit proinflammatory responses in macrophages in both cAMP-independent and GPR81-independent manners (36). Similarly, natural killer (NK) cells, when exposed to lactic acid or lactate, significantly reduce their cytotoxic activity, an effect mediated by downregulation of the NK-activating receptor NKP-46 (68).

Anti-inflammatory effect of lactate has been nicely demonstrated by Hoque et al. (65) in a study showing that transient lactate exposure suppresses inflammation and tissue damage in chemically induced pancreatitis and hepatitis models. The effects are mediated through interactions of lactate-GPR81 and GPR81-arrestin β2 in monocytes and macrophages, leading to inhibition of TLR4- and inflammasome-mediated induction of mediators (IL1B, Nlrp3, and Casp1), activation of NF-κB, and cleavage of CASP1. The anti-inflammation and tissue protection attributable to the lactate-GPR81 interaction is via a noncanonical pathway independent of cAMP/ PKA signaling (65). Similar lactate-mediated anti-inflammatory response was also observed in a murine model of colitis [induced by 2,4,6-trinitrobenzene sulfonic acid (TNBS)] (71). In that model, lactate administration prevented the serum IL-6 elevation and protected against microbial translocation from the gut to the liver. These results are consistent with previous studies showing lactate, along with short-chain fatty acids, prevents TLR-mediated activation of macrophages and dendritic cells (70).

Since inflammatory reactions also occur in neurons (122) and several of the same mediators (i.e., TLRs and interleukins) also operate in the brain, lactate-mediated anti-inflammatory effects are implicated in brain pathology. To this extent, NMDA receptors have been shown to confer protection against inflammatory tissue damage (38) through mechanisms reminiscent of those of GPR81 (65), suggesting a potential synergistic interaction between GPR81 and NMDA receptors, which, coincidentally, are colocalized at the postsynaptic spine. That said, whether the tissue-protective action of lactate actually occurs in the brain is unclear and requires further investigation. Moreover, the “noncanonical” activities induced by lactate-GPR81 and its pathophysiological significance should be explored.

**Memory Formation and Neuro Protection**

It is well established that short-term memory can be formed by modifications of existing proteins, whereas long-term memory requires activation of gene cascades, including expression of early immediate genes and new protein synthesis. Aerobic glycolysis in the brain is pivotal in neotenous gene (109) expression, tightly linked to the development of synapses, neuron projections, and learning (56). Specifically, lactic acid derived from glycolysis in astrocytes is transported via MCTs to neurons where lactate exerts signaling functions (9) and stimulates gene expression related to long-term memory formation (9, 96, 133). Such effects are dependent on intact lactate transporters MCT1, MCT2, and MCT4. Disrupting these MCT expressions causes
defects in memory consolidation, leading to amnesia. In a recent study, Yang et al. showed that lactate stimulates plasticity-related early immediate gene expression in neurons, including Arc (activity-regulated cytoskeletal protein), cFos (a proto-oncogene), and Zif/268 (or Egr1, early growth response 1) (158). The upregulated expression is induced by lactate through modulating the NMDAR (glutamate receptor: N-methyl-D-aspartate receptor) activity. NMDARs are glutamate-gated ion channels critical in the regulation of synaptic plasticity related to learning and long-term memory formation. The lactate-mediated effects are associated with an increased cellular NADH, lactate-specific intracellular calcium elevation, and subsequent activation of Erk1/2 pathways (158). Hence, lactate can exert a signaling role, important, indeed critical, in learning and memory formation (133). Whether GPR81 participates in these memory-forming pathways requires investigation.

Acute stress induces cytosolic cAMP elevation via activating the adrenergic system, which is associated with an enhanced cognitive function. Chronic stress, however, is associated with a sustained cAMP elevation and cognitive impairment (92). Aging is related to overactivation of certain signaling pathways in the brain, including overactivation of glutamate receptors and glutamate-mediated signaling (143). Lactate-induced GPR81 activation, by reducing cAMP, could potentially provide a modulatory mechanism to the overactivated signaling cascades and thus might prevent memory decline and senile dementia. Moreover, through positively influencing MCT1 and PGC-1α expression, lactate activates the mitochondrial biogenesis, which promotes healthy aging (119). Taken together, cumulative data strongly support a role for lactate in stimulating neuronal plasticity, enhancing memory, and enhancing neuronal protection.

Wound Healing

In a healing wound, aerobic glycolysis is prominent (53, 135). Lactic acid in the interstitial fluids of healing wounds amount up to 5–15 mM (67). Porporeto et al. (112) showed that endogenous lactic acid and exogenous lactate [delivered locally and systemically (~4 mM) through poly-D, L-lactide-co-glycolide, also known as PLGA] can promote reparative angiogenesis with recruitment of endothelial progenitor cells, activate procollagen factors, and enhance extracellular matrix deposition in mice with ischemic wounds. Lactate accelerated wound healing and prevented ischemic skeletal muscle atrophy (112). In line with these findings, Chereddy et al. (24) have recently shown that combined local delivery of lactate and VEGF (encapsulated in PLGA nanoparticles) in a splint mouse full-thickness excisional model can accelerate healing of both non-diabetic and diabetic wounds. These effects are consistent with previous data showing that lactic acid stimulates angiogenesis in wounds by increasing VEGF in the infiltrating microvessels (26). Cellular lactic acid accumulation also raises NADH-to-NAD⁺ ratio, removing the inhibitory force of poly-ADPR on VEGF synthesis and of mono-ADPR on VEGF activity (125). Additionally, lactic acid enhances collagen deposition (26), further promoting wound healing (135). Collectively, in wound healing, lactic acid/lactate is bioactive. Exogenous lactate delivery should be explored as a promising therapy in the management of non-healing wounds.

Ischemic Tissue Injury

In the setting of acute tissue ischemia and ischemia-induced lactic acid generation, an important cellular response is activation of the plasma membrane sodium proton exchangers (NHEs) (97, 98), primarily NHE1. NHE1, cloned in the 1990s (48, 72), is the major isoform of the nine NHE family isoforms (NEH1-5 are expressed in the plasma membrane, and NHE6-9 are expressed in the intracellular organelles). NHE1 contains 12 transmembrane helices. Its NH₂ terminus constitutes the ion translocation domain; the cytoplasmic hydrophilic COOH terminus contains binding sites for various regulatory proteins. NHE1 is ubiquitously expressed and plays a dominant role in the regulation of intracellular pH (pHi), cell differentiation, and cell volume. In the kidneys and intestinal tract, NHE1 also mediates transepithelial Na⁺ and HCO₃⁻ absorption (129).

In acute tissue ischemia, NHE1, through Na⁺-H⁺ exchange, increases intracellular Na⁺, which leads to Ca²⁺ overload due to CNX-mediated Ca²⁺-Na⁺ exchange and cell death (115). These detrimental effects can be prominent in the brain and heart (7, 159). Pharmacological NHE1 inhibition (amiloride and cariporide) attenuates ischemia/reperfusion-induced myocardial and brain injury in animal models (4, 23, 66, 117, 160). Moreover, NHE1 deletion has been associated with neuroprotective effects in cerebral ischemia (10, 95, 144). In addition, in the setting of severe sepsis-related lactic acidosis, animals pretreated with NHE-1 blockers develop less sepsis-related lactic acidosis, animals pretreated with NHE-1 blockers develop less hemodynamic instability and better survival compared with their non-treated counterparts (128, 152, 153).

GPR81-mediated signaling activated by lactate also has been shown to exacerbate ischemic brain injury. GPR81 blockade (by 3-OBA) can significantly attenuate the ischemic brain injury in the oxygen-glucose deprivation and middle cerebral artery occlusion models (126). The neuroprotective effects are mediated, at least in part, through curtailing neuro-
nal apoptosis from the ERK signaling, which is downstream of the GPR81 activation. The authors also provided evidence suggesting that a relatively low concentration of lactate (~1–3 mM) may contribute to neuronal injury through GPR81 activation, whereas a high concentration (~20 mM) may contribute to neuroprotection by acting as a fuel in the setting of energy crisis due to ischemia (126).

**Cancer Growth and Metastasis**

Cancer cells, especially rapid growing type, are known to constitutively carry out aerobic glycolysis (Warburg effect). Lactic acid surrounding the tumor tissues can reach up to 40 mM (normal tissue: 1.8–2.0 mM) (142). High levels of insulin, known to promote glycolysis, in diabetes or in individuals with an insulin-resistant state have been associated with an increased cancer risk (155). Lactic acidosis in cancer patients is correlated with rapid cancer growth, metastasis, and poor survival.

Cancer cells rely on MCTs to transport lactic acid. MCT1 and MCT4 are robustly expressed in various cancers. Lactic acid efflux via MCTs contributes to the characteristic pH gradient reversal, an acidic pH_e, and neutral or alkaline pH_i in tumors (**FIGURE 2**). In addition to lactic acid, the reversal is also contributed by a collective array of H^+ extrusion pumps and transporters, including NHEs, vacular H^+ -ATPase, and carbonic anhydrases 9 and 12 (27, 43, 57, 140, 141). Acidic extracellular microenvironment promotes cancer growth and invasion through 1) extracellular matrix remodeling by proteinase activation, 2) increasing angiogenesis via the release of VEGF, 3) increasing cancer cell motility, and 4) inhibiting the immune response to tumor antigens (17, 20, 45, 49, 50, 84, 104, 118, 130, 157). The harsh acidic microenvironment also selects the most malignant cancer cells (151). Intracellular alkalization promotes cell transformation and alters its energetic metabolism (97), favoring tumor growth. These effects are exemplified by experiments reported by Estrella et al. showing that, in a combined immuno-deficient (SCID) mouse model, acidic pH_e of peritumoral tissues was coincident with the location of subsequent tumor invasion, and bicarbonate treatment reduced the pH gradient and prevented cancer cell invasion (37).

Cytosolic lactic acid in cancers has been shown to impact several critical biologically significant activities (30). Lactate is capable of activating HIF-1α, independent of hypoxia (25, 28, 93, 94, 131) (**FIGURE 2**). In endothelial cells, MCT1-mediated lactic acid uptake causes NF-κB/IL8 activation (136). The combined activation of HIF-1α and NF-κB/IL8 leads to angiogenesis. Coexpression of

**FIGURE 2.** Lactic acid in normal and cancer cells

In cancer cells, lactate, after conversion into pyruvate, binds prolylhydroxylation and activates HIF-1α in the presence of O_2, inducing angiogenesis. See text for details.
CD147, MCTs, and multiple drug-resistance proteins has been associated with aggressive ovarian cancer progression (21). MCT expression is also associated with aggressive phenotype in prostate cancer (108).

In contrast to the cellular injurious effects of GPR81 signaling in ischemic brain (126), lactate-induced GPR81 activation promotes cancer growth. Roland et al. (120) found that GPR81, expressed in multiple cancer cell lines including colon, breast, lung, hepatocellular, salivary gland, cervical, and pancreatic cancers, regulates expression of genes involved in lactate uptake and metabolism, including MCTs. GPR81 silencing in a xenografted cancer model dramatically reduced tumor growth and metastasis. The GPR81 deletion also reduced expression of PCG-1α, MCT1, MCT4, and CD-147. These results indicate that lactate-induced GPR81 activation is a survival pathway for cancer. The details of this pathway are yet to be elucidated.

Lactic acid also contributes to the reduced immune competency of the tumor-infiltration host macrophages and lymphocytes (40, 101, 127). In tumor-infiltrating T lymphocytes, extracellular acidification diminishes STAT5 and ERK activation, and the expression of IL-2Rα (CD25) and TLR, inducing an anergic state. In dendritic cells, extracellular acidity interferes with lactic acid extrusion; the intracellular lactic acid accumulation contributes to the anergic phenotype. Buffering extracellular acidity abolished these abnormalities (17, 33). A majority of chemotherapeutic agents are weak bases and are substantially ionized in an acidic milieu. Ionization prevents entry of these agents into the tumor cells, curtailing their efficacy. Acid buffering thus is expected to enhance chemosensitivity. Consistent with this concept, inhibition of lactate fluxes in cell lines of human cancers and mouse xenograft models potentiates chemosensitivity (5, 34). Inhibition of MCT1 and its ancillary protein CD147 in rodent models (64, 124, 132) and in several human trials (12, 63, 154, 156) has also been shown to deter cancer growth. Thus strategies to neutralize extracellular acidity and interfere with lactic acid flux provide a unique and exploitable avenue for cancer treatment.

Some Remaining Questions

Although impressive advances have been made, many questions remain. For instance, the noncanonical pathway of GPR81 activated by lactate has only recently been recognized and must be characterized; the reasons underlying cardiac dysfunction in a lactate-deprived setting are unclear, and whether GPR81 is involved in the process has yet to be elucidated; kidneys contribute to systemic glucose supply to varying degrees via gluconeogenesis utilizing lactic acid, although how such an on-demand process is regulated remains unclear; and, although GPR81 is found in the intracellular organelles, implying intracellular lactate trafficking, details of the trafficking mechanisms and its regulation are yet to be uncovered. CD44 has been shown to be associated with the MCT1/MCT4/CD147 complex (8), but whether it can function as another MCT ancillary protein is unknown. A distinct lactate receptor in the locus coeruleus has been described (134), which increases rather than suppresses cAMP level; further research is required to confirm the findings. In the brain, lactate, through GPR81, is capable of linking synaptic function, energy metabolism, and cerebral blood flow. The precise lactate-evoked signaling mechanisms in this process have yet to be elucidated. Many proposed mechanisms are speculative. Similarly, the mechanisms underlying opposite effects of mildly vs. highly elevated lactate in ischemic brain are speculative and invite further study. Last, the extent to which raising pH would lead to a better intracellular distribution of chemotherapeutic agents in cancer needs to be confirmed. That said, emerging modern technologies, especially several newer in vivo pH-monitoring techniques (6, 22, 114, 123), are expected to greatly facilitate research in this field to unveil novel information to address the existing questions.

Conclusions

It has become clear that lactic acid is a signaling molecule and a powerful regulator in multiple conditions of health and disease, including energy regulation, immune modulation, memory formation, wound repair, ischemic tissue injury, and cancer progression, and is far from being merely an inert energy donor. In only a few areas of medicine have our knowledge advances reached to such a degree toward fundamentals of the molecule and its associated pathways. Nonetheless, a large number of questions remain. Further research and a better understanding of lactic acid will likely impact medical practice and benefit patient care. ■
References


