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The Role of Lactate Signaling and Cancer-Associated Fibroblasts in Mediating Tumor Progression

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ABSTRACT

Once considered a wasteful byproduct of metabolism, lactate is now recognized as both a metabolic intermediate and a signaling molecule across many cell types within the tumor microenvironment. Evidence was synthesized to evaluate how tumor-derived lactate influences signaling in surrounding cancer-associated fibroblasts (CAFs), contributes to tumor progression, and may serve as a potential therapeutic target. Relevant primary and review articles were identified through PubMed and reference lists from relevant reviews and organized into four themes: lactate production in cancer metabolism, lactate-mediated signaling, tumor–CAF communication, and therapeutic targeting of lactate pathways. The reviewed evidence indicates that tumor-derived lactate can promote cancer progression through both metabolic and signaling mechanisms. Lactate can alter CAF metabolism and signaling, contributing to fibrosis, inflammatory signaling, and immune suppression, while experimental studies suggest that targeting lactate production or transport may have therapeutic potential. However, these effects vary across cancer types, emphasizing the need for tumor-specific approaches to lactate-targeted therapy.

INTRODUCTION

Cancer is a complex disease characterized by many hallmarks, most notably uncontrolled cell growth. More recently, it has become clear that tumor progression depends on more than the intrinsic activity of cancer cells. Initiating tumor cells interact with the surrounding microenvironment, comprising immune cells, stromal cells, endothelial cells, and the extracellular matrix. These interactions significantly alter the metabolic and immune profile of the tumor, setting the stage for malignant programs that mediate disease progression and treatment resistance (Hanahan, 2022). Understanding the signals exchanged between cancer cells and their surrounding environment is imperative for developing effective therapies (Hanahan, 2022; Sahai et al., 2020).

One major way cancer cells interact with other cellular constituents of the tumor microenvironment is through metabolic signaling. Early evidence of the altered metabolism of cancer cells came from the observation of Otto Warburg and colleagues that tumor tissues consumed high amounts of glucose and produced large amounts of lactate even when oxygen was available, a metabolic phenotype known as the

Warburg Effect (Warburg et al., 1927; Koppenol et al., 2011; Liberti & Locasale, 2016). This metabolic phenotype increases lactate production and release into the tumor microenvironment, establishing an early connection between cancer metabolism and lactate accumulation in tumors (Pérez-Tomás & Pérez-Guillén, 2020).

Lactate was not always understood as an important biomolecule. Traditionally, lactate accumulation during metabolic stress led researchers to view lactate as a toxic waste product of anaerobic metabolism (Ferguson et al., 2018; Philp et al., 2005). Later research challenged this idea as lactate was demonstrated to move between cells and tissues through dedicated transport proteins called monocarboxylate transporters, or MCTs (Philp et al., 2005). Once lactate enters another cell, it can be enzymatically oxidized into pyruvate and used for energy production. In the liver, lactate facilitates glucose regeneration through the Cori cycle (Brooks, 2020; Rogatzki et al., 2015). These conserved mechanisms for transporting and reusing lactate suggest that cells use lactate as a flexible metabolic intermediate that participates in energy balance across different cell and tissue types.

Beyond its role as a metabolic intermediate, recent research has explored the potential for lactate to function as a signaling molecule. Lactate has been reported to drive changes in cell behavior via transporter-mediated uptake, receptor signaling, and gene regulation (Ishihara et al., 2022; Zhang et al., 2019). These effects can occur within cancer cells themselves and nearby non-tumor cells. One of the prominent stromal cell types involved in this communication is the cancer-associated fibroblast (CAF) (Sahai et al., 2020). CAFs are non-cancerous stromal cells within the tumor microenvironment that can be altered by signals from nearby tumor cells and can support tumor growth, fibrosis, immune suppression, and therapy resistance (Sahai et al., 2020). These tumor-supportive cells are especially significant because they can reshape the extracellular matrix, release tumor-promoting inflammatory signals, and limit the antitumor activity of immune cells (Sahai et al., 2020; Gu et al., 2024). Recent studies report a major role for lactate secreted from tumor cells to stimulate these tumorigenic functions in CAFs, underscoring the dynamic contributions of the tumor microenvironment to malignancy.

Recent work has begun to identify mechanisms connecting tumor-derived lactate, CAF signaling, immune suppression, and tumor progression. Understanding these interactions may also reveal whether lactate production, transport, or signaling can be selectively targeted for cancer therapy.

METHODS

A literature search was conducted from May to July 2026 using PubMed. Reference lists from relevant review articles were also screened. Most selected sources were published between 2000 and 2026, with older foundational studies included for historical context. Initial searches focused on background information about lactate metabolism and cancer metabolism using keywords such as “lactate metabolism,” “lactate signaling,” “Warburg effect,” and “lactate tumor microenvironment.” Additional searches narrowed the review toward tumor-stromal interactions using terms such as “cancer-associated fibroblasts,” “lactate cancer-associated fibroblasts,” “tumor-derived lactate,” “immune suppression,”

"MCT1," "MCT4," "GPR81," "histone lactylation," "LDHA," and "lactate cancer therapy." Search results were first screened by title, followed by review of the abstracts of potentially relevant articles. Full-text articles were then examined and selected based on their relevance to lactate production and signaling, cancer-associated fibroblast behavior, immune suppression, tumor progression, and therapeutic targeting of lactate pathways. Review articles were used mainly for background information, while primary research articles were used to analyze current mechanisms and experimental evidence. Over 40 articles were consulted during the research process. Of these, 26 unique sources were included in the final manuscript, of which 22 were cited in the thematic sections.

LITERATURE REVIEW

The current literature can be organized into four interconnected areas: lactate production in cancer metabolism, lactate-mediated signaling, communication between tumor cells and CAFs, and therapeutic targeting of lactate pathways. Examining these themes together helps clarify how increased lactate production progresses from a metabolic feature of cancer to a potentially therapeutically actionable mechanism that influences surrounding cells.

Theme 1: Lactate Production in Cancer Metabolism

Glucose metabolism begins with glycolysis, a process in which glucose is broken down in the cytoplasm to form pyruvate. Under aerobic conditions, pyruvate can enter the tricarboxylic acid cycle and electron transport chain in the mitochondria to generate ATP (Ferguson et al., 2018; Liberti & Locasale, 2016). Alternatively, lactate dehydrogenase (LDH) can convert pyruvate to lactate while regenerating NAD+, fueling glycolysis. In cancer cells, this conversion remains particularly elevated in the presence of oxygen (Liberti & Locasale, 2016; Ferguson et al., 2018). Once produced, lactate has two fates: 1) conversion back to pyruvate by LDH for use in oxidative metabolism and 2) transport outside of the cell through monocarboxylate transporters (MCTs). In highly glycolytic cancer cells, lactate is often exported into the extracellular environment, where it is taken up and used by neighboring cells (Philp et al., 2005; Pérez-Tomás & Pérez-Guillén, 2020). These processes connect the metabolic adaptations associated with the Warburg Effect to changes in the surrounding tumor microenvironment.

A major part of this process depends on lactate dehydrogenase (LDH). LDH subunits encoded by the LDHA and LDHB genes combine to form distinct LDH isoenzymes. Disrupting both LDHA and LDHB in human colon adenocarcinoma and mouse melanoma cells eliminated lactate secretion and shifted the cells toward oxidative metabolism (Ždralević et al., 2018). These double-knockout cells proliferated more slowly under normoxic conditions and were strongly restricted under hypoxic conditions. These findings support the idea that lactate production helps tumor cells maintain growth, particularly under hypoxic conditions.

Lactate production depends on a larger metabolic network. In tumor and normal cell lines, high concentrations of extracellular pyruvate inhibited LDH activity and decreased lactate production in an MCT1-dependent manner (Rao et al., 2021). Pharmacologic or genetic inhibition of MCT1-mediated

pyruvate uptake reduced this effect, indicating that intracellular pyruvate availability and transporter activity can influence lactate production. Overall, lactate levels are regulated by LDH activity, MCT expression, nutrient availability, and the surrounding cellular environment. Increased glycolysis and LDH activity drive high lactate production in many cancers, while MCT-mediated transport regulates lactate movement across the cell membrane.

Theme 2: Lactate as a Signaling Molecule

Elevated lactate secretion from cancer cells raises the possibility that lactate functions not only as a metabolite but also as a signaling molecule within the tumor microenvironment. CAFs and other stromal cells can take up and metabolize lactate released by glycolytic tumor cells (Rattigan et al., 2012). In pancreatic cancer co-cultures containing cancer cells and CAFs, CAFs consumed cancer-derived lactate through MCT1 (Kitamura et al., 2023). These findings demonstrate that tumor-derived lactate can be exchanged between cancerous and non-cancerous cells rather than simply accumulating as metabolic waste.

Lactate can also signal through GPR81, a G-protein coupled cell-surface receptor. GPR81 was highly expressed in human breast cancer cell lines, mouse tumor models, and human breast tumor samples. Silencing GPR81 reduced lactate production, glycolytic activity, proliferation, migration, invasion, and tumor growth in mice (Ishihara et al., 2022). GPR81 knockdown also increased apoptosis in MCF-7 breast cancer cells both *in vitro* and in xenograft tumors (Lee et al., 2016). These findings support GPR81 as a receptor-mediated pathway through which extracellular lactate can influence cancer-cell metabolism and tumor-promoting behavior.

Lactate can also influence gene regulation through protein lactylation. Lactyl groups can modify lysine residues on histone proteins, which package DNA into chromatin, and thereby influence transcription (Zhang et al., 2019; Wang et al., 2023). Histone lactylation has been identified in both mouse and human cells, and increased lactylation in a macrophage model was associated with changes in genes involved in cellular homeostasis (Zhang et al., 2019). Subsequent work has also identified lactylation on non-histone proteins, including mitochondrial proteins in rat brain tissue, suggesting that lactylation may influence cellular metabolism in addition to gene regulation (Yao et al., 2023; Wang et al., 2023). Overall, these findings establish lactylation as another mechanism through which elevated lactate levels can alter cellular function.

Subsequent studies have begun to clarify how lactylation-regulated gene expression can contribute to tumor progression. In breast cancer cells, increased lactate promoted H3K18 histone lactylation near the c-Myc promoter, thereby increasing c-Myc expression in breast cancer cells (Pandkar et al., 2023). c-Myc is a transcription factor encoded by the *MYC* proto-oncogene that regulates genes involved in cell growth, proliferation, and metabolism (Pandkar et al., 2023). This provides a direct example of lactate-driven epigenetic regulation contributing to cancer-promoting gene expression. In non-small cell lung cancer cells, lactate-induced histone lactylation decreased the transcription of several glycolytic genes while increasing the transcription of genes involved in the TCA cycle (Jiang et al., 2021). Collectively, these studies demonstrate that lactate-induced histone lactylation can increase or decrease the expression of

specific genes, while the resulting gene-regulatory changes supported tumor-promoting behavior in breast and lung cancer models (Pandkar et al., 2023; Jiang et al., 2021).

Building on these findings, several signaling mechanisms emerge through which lactate can influence cell behavior, including transporter-mediated uptake, GPR81 receptor signaling, and histone lactylation. These mechanisms allow extracellular lactate to affect both cellular metabolism and gene regulation, providing several ways in which tumor-derived lactate may influence surrounding cells within the tumor microenvironment.

Theme 3: Lactate-Mediated Communication Between Tumor Cells and CAFs

Cancer-associated fibroblasts are among the main stromal cell types in the tumor microenvironment that have been co-opted by the presence of tumor cells to support their progression by altering the extracellular matrix, releasing inflammatory signals, and affecting immune-cell activity (Sahai et al., 2020). Since CAFs are located near tumor cells, they are exposed to tumor-derived metabolites such as lactate. In glioblastoma models, elevated lactate increased expression of the lactate transporter MCT1 and the lactate receptor GPR81, potentially enhancing cellular responses to extracellular lactate (Longhitano et al., 2022). More specifically, within the stromal compartment, lactate secreted from cancer cells can be taken up by nearby CAFs, leading to altered gene expression and inflammatory signaling profiles (Kitamura et al., 2023; Rattigan et al., 2012).

In pancreatic cancer, CAFs with restricted glucose availability were able to use lactate from glycolysis-enhanced cancer cells as fuel (Kitamura et al., 2023). Lactate-stimulated CAFs also helped maintain a fibrotic and immunosuppressive tumor microenvironment. These findings establish a pathway through which tumor-derived lactate can promote tumor progression by altering stromal-cell metabolism and signaling.

In breast cancer models, hypoxia increased lactate secretion by MDA-MB-231 and MCF-7 tumor cells, while lactate exposure increased *MCT1* expression and promoted migration in human mesenchymal stem cells. Most directly, carbon-13 nuclear magnetic resonance tracing detected the conversion of carbon-13-labeled lactate into carbon-13-labeled α-ketoglutarate in mesenchymal stem cells and CAFs, indicating that these stromal cells took up lactate and routed it into the TCA cycle for oxidative metabolism. These findings supported a tumor–stroma lactate shuttle in which glycolytic tumor cells export lactate and nearby stromal cells use it as an energy source (Rattigan et al., 2012). In a lung cancer model, tumor-derived lactate activated CAFs that secreted interleukin-8 (IL-8), an inflammatory signaling molecule that increased macrophage recruitment and promoted an immunosuppressive macrophage state (Gu et al., 2024). These results link lactate abundance to CAF-mediated immunosuppression within the tumor microenvironment.

These studies link tumor metabolism to CAF-driven changes in the tumor microenvironment. Tumor cells produce lactate through altered metabolism, and CAFs can take up or respond to that lactate, promoting fibrosis, inflammatory signaling, macrophage recruitment, and other tumor-supportive changes.

Tumor-derived lactate can therefore alter stromal-cell metabolism and inflammatory signaling in ways that favor tumor progression.

Theme 4: Therapeutic Targeting of Lactate Pathways

Because lactate production and transport are connected to tumor progression, lactate pathways have become possible targets for cancer therapy. One approach is to target lactate transport through monocarboxylate transporters such as MCT1 and MCT4 (Bola et al., 2014; Polański et al., 2014; Qian et al., 2023). These transporters are important because they enable lactate to move into or out of cells, thereby helping maintain cancer cell metabolism and lactate exchange within the tumor microenvironment. If lactate transport is blocked, intracellular lactate can accumulate in cancer cells, disrupting metabolic homeostasis and reducing proliferation; under hypoxic conditions, MCT1 inhibition has also induced nonapoptotic cell death in small cell lung cancer models (Polański et al., 2014).

AZD3965, an experimental inhibitor of the lactate transporter MCT1, altered lactate transport and glycolytic metabolism in small cell lung cancer and gastric cancer cell lines (Bola et al., 2014). In H526 small cell lung cancer xenografts, AZD3965 alone delayed tumor growth, while a parallel experiment using the same xenograft model found that combining AZD3965 with fractionated radiotherapy produced a greater tumor-growth delay than radiation alone. MCT1 inhibition with AZD3965 also reduced tumor growth and increased intratumoral lactate in small cell lung cancer models (Polański et al., 2014). Together, these studies provide preclinical evidence for targeting lactate transport in small cell lung cancer, particularly in tumors that depend strongly on MCT1-mediated lactate transport.

Targeting lactate pathways may also affect immune suppression in the tumor microenvironment. In one lung adenocarcinoma model, increased MCT4-dependent lactate export contributed to suppression of antitumor immunity (Qian et al., 2023). In pancreatic cancer, lactate-stimulated CAFs increased interleukin-6 (IL-6), a proinflammatory cytokine; inhibition of LDHA in cancer cells with small-molecule FX11 reduced tumor IL-6 levels and CAF abundance (Kitamura et al., 2023). These findings connect tumor-derived lactate to immune suppression within the tumor microenvironment. If tumor-derived lactate weakens antitumor immune responses, then blocking lactate export could make the tumor microenvironment less favorable for cancer progression and potentially improve immunotherapeutic efficacy. Inhibiting MCT1 in CAFs prevented lactate-induced CAF proliferation under glucose-limited conditions (Kitamura et al., 2023). However, among the studies reviewed here, there is limited evidence directly testing whether inhibition of lactate export from cancer cells prevents CAFs from developing tumor-promoting properties.

Targeting lactate metabolism also has limitations. Lactate has important physiological roles in normal tissues, where it can serve as a substrate for oxidative metabolism through conversion to pyruvate and participate in metabolic exchange between cells and tissues (Brooks, 2020; Philp et al., 2005). Some tumors appear to depend more strongly on particular lactate pathways. For example, the small cell lung cancer models reviewed here showed dependence on MCT1-mediated lactate transport (Bola et al., 2014; Polański et al., 2014). However, these dependencies are not established across all cancer types. Identifying which tumors rely most strongly on specific lactate pathways will be important for matching

lactate-targeted treatments to appropriate patients. Tumors can also adapt metabolically, which means blocking one lactate pathway may not be enough in every cancer type. Overall, lactate-targeted therapy appears promising, but it may work best when combined with other treatments or when matched to tumors that strongly depend on lactate production, secretion, or transport.

These therapeutic studies connect back to the main focus of this review. If lactate helps tumor cells communicate with surrounding cells, contributes to immune suppression in certain tumor contexts, and shapes the tumor microenvironment, then targeting lactate pathways could weaken tumor-supportive conditions. Thus, further mechanistic research into lactate production, transport, and signaling within the tumor microenvironment would help inform potential combination therapies involving inhibition of lactate export from cancer cells.

DISCUSSION

The evidence reviewed supports an active role for lactate in tumor progression by linking altered cancer metabolism to changes in the surrounding microenvironment. Across breast, pancreatic, and lung cancer models, tumor-derived lactate can serve as a metabolic substrate for stromal cells, specifically CAFs to promote fibrosis, inflammatory signaling, and immune suppression (Rattigan et al., 2012; Kitamura et al., 2023; Gu et al., 2024). These findings suggest that CAF-mediated effects are one important component of lactate-driven tumor progression, although lactate can also act directly on cancer and immune cells.

One therapeutic implication of the reviewed evidence is that targeting lactate production, transport, or signaling may disrupt tumor-supportive communication within the microenvironment. Inhibiting LDH or monocarboxylate transporters could reduce the ability of tumor cells to produce, export, or reuse lactate. For example, the LDHA inhibitor FX11 reduced tumor growth and improved antitumor immunity in CAF-rich pancreatic tumors, supporting the idea that disrupting tumor-derived lactate can alter both stromal and immune components of the microenvironment (Kitamura et al., 2023). However, the effects of these interventions may vary depending on transporter expression, cancer type, and immune context (Bola et al., 2014; Polański et al., 2014; Qian et al., 2023). Researchers should also compare the effects of targeting key regulators of lactate metabolism and signaling, such as LDH, MCT1, MCT4, and GPR81, while investigating whether histone lactylation represents an additional therapeutic target. Using 2D co-culture models and 3D organoid systems would help distinguish which cell types are most affected by suppression of lactate production and export.

CAFs themselves represent a separate therapeutic target because of their lactate-dependent and -independent contributions to tumor progression, as demonstrated by the immunosuppressive phenotypes induced by a CAF-rich microenvironment (Kitamura et al., 2023; Gu et al., 2024). However, CAFs should not be treated as a single cell population, because different CAF subtypes may have distinct or even opposing functions within the same tumor (Sahai et al., 2020). Some CAF populations can promote fibrosis, inflammatory signaling, and immune suppression, while others may restrain tumor growth or support antitumor immune response. Such heterogeneity limits the usefulness of broadly targeting CAFs. Single-cell and spatial analyses could help determine which CAF and immune-cell populations respond most strongly to tumor-derived lactate.

Important questions therefore remain. Which CAF subtypes depend most strongly on tumor-derived lactate, and are their tumor-supportive effects driven primarily by lactate uptake or signaling? Can lactate-responsive CAF populations be targeted without disrupting tumor-restraining fibroblast populations? Addressing these questions may enable more selective therapeutic strategies.

There are also important limitations in the current evidence. First, many studies are based on specific cancer types, such as pancreatic cancer, breast cancer, or lung cancer. These tumors differ in metabolism, transporter expression, CAF composition, and immune environment, so findings from one cancer type may not apply equally to another. For example, if inhibiting a lactate-related pathway weakens antitumor immune activity in a particular tumor, that treatment may not be suitable for combination with immunotherapy. Further studies should first determine whether the intervention strengthens or weakens antitumor immune activity in that specific tumor context. A detailed understanding of these tumor-specific metabolic and immune differences will be important for identifying which patients are most likely to benefit from lactate-targeted therapies. More broadly, lactate-targeted treatments should be evaluated according to cancer type, based on transporter expression, CAF composition, and immune environment.

Second, lactate has several functions at once: it can act as a metabolic fuel, signaling molecule, acidifier, and substrate for lactylation. It can therefore be difficult to distinguish effects caused directly by lactate signaling from those caused indirectly by changes in pH, metabolism, or nutrient availability. In pancreatic cancer models, CAFs used tumor-derived lactate as a metabolic fuel through the TCA cycle, while lactate exposure also increased IL-6 production and contributed to suppression of cytotoxic immune-cell activity (Kitamura et al., 2023). Because these metabolic and signaling effects occurred together, the resulting tumor-promoting phenotype cannot necessarily be attributed to one lactate-mediated mechanism alone. Lactate tracing could help identify which cells produce, export, and consume lactate and clarify whether particular biological effects result primarily from lactate metabolism, signaling, or both.

A further limitation is that much of the therapeutic evidence remains preclinical. The reviewed studies used combinations of cancer cell lines, animal models, xenografts, and tumor-tissue analyses, but these systems may not fully reproduce the stromal and immune complexity of human tumors. Results observed under controlled experimental conditions may therefore differ from responses in patients. Patient-derived organoids, tumor explants, and models containing both stromal and immune cells could help determine whether findings from cell lines and animal models are translatable to human tumors. Studies of LDH or MCT inhibition also need to determine how these treatments affect healthy cells, because normal tissues and immune cells use lactate-related pathways as part of regular metabolism (Ždralević et al., 2018; Bola et al., 2014; Polański et al., 2014; Qian et al., 2023). Thus, translating lactate-targeted therapies to the clinic will require models that accurately recapitulate the heterogeneity of the tumor microenvironments observed in humans.

Overall, the evidence supports the conclusion that lactate promotes tumor progression by linking altered tumor metabolism to changes in gene expression, CAF behavior, fibrosis, and immune suppression.

However, lactate does not act through one universal mechanism, and CAFs are not the only cells that respond to it. Future work disentangling the direct and indirect consequences of lactate signaling in tumor cells, CAFs, and immune cells is therefore crucial for understanding the tumor-promoting properties of lactate and identifying which patients may benefit from targeting it.

CONCLUSION

Tumor-derived lactate contributes to cancer progression partly by altering CAF metabolism and signaling within the tumor microenvironment. CAFs can take up or respond to lactate released by cancer cells, supporting fibrosis, inflammatory signaling, immune suppression, and other tumor-promoting conditions. These findings support therapeutic strategies targeting lactate production, transport, or signaling, although such approaches will need to account for differences among cancer types and normal physiological uses of lactate. Future research should determine which lactate-dependent pathways are most important in specific tumors and which patients are most likely to benefit from targeting them. Overall, lactate acts as a tumor-promoting factor in the cancer contexts reviewed, but its effects remain complex and context-dependent.

REFERENCES

Bola, B. M., Chadwick, A. L., Michopoulos, F., Blount, K. G., Telfer, B. A., Williams, K. J., Smith, P. D., Critchlow, S. E., & Stratford, I. J. (2014). Inhibition of monocarboxylate transporter-1 (MCT1) by AZD3965 enhances radiosensitivity by reducing lactate transport. Molecular cancer therapeutics, 13(12), 2805–2816. https://doi.org/10.1158/1535-7163.MCT-13-1091

Brooks G. A. (2020). Lactate as a fulcrum of metabolism. Redox biology, 35, 101454. https://doi.org/10.1016/j.redox.2020.101454

Ferguson, B. S., Rogatzki, M. J., Goodwin, M. L., Kane, D. A., Rightmire, Z., & Gladden, L. B. (2018). Lactate metabolism: historical context, prior misinterpretations, and current understanding. *European journal of applied physiology*, *118*(4), 691–728. https://doi.org/10.1007/s00421-017-3795-6

Gu, X., Zhu, Y., Su, J., Wang, S., Su, X., Ding, X., Jiang, L., Fei, X., & Zhang, W. (2024). Lactate-induced activation of tumor-associated fibroblasts and IL-8-mediated macrophage recruitment promote lung cancer progression. *Redox biology*, *74*, 103209. https://doi.org/10.1016/j.redox.2024.103209

Hanahan D. (2022). Hallmarks of Cancer: New Dimensions. *Cancer discovery*, *12*(1), 31–46. https://doi.org/10.1158/2159-8290.CD-21-1059

Ishihara, S., Hata, K., Hirose, K., Okui, T., Toyosawa, S., Uzawa, N., Nishimura, R., & Yoneda, T. (2022). The lactate sensor GPR81 regulates glycolysis and tumor growth of breast cancer. *Scientific reports*, *12*(1), 6261. https://doi.org/10.1038/s41598-022-10143-w

Jiang, J., Huang, D., Jiang, Y., Hou, J., Tian, M., Li, J., Sun, L., Zhang, Y., Zhang, T., Li, Z., Li, Z., Tong, S., & Ma, Y. (2021). Lactate Modulates Cellular Metabolism Through Histone Lactylation-Mediated Gene Expression in Non-Small Cell Lung Cancer. *Frontiers in oncology*, *11*, 647559. https://doi.org/10.3389/fonc.2021.647559

Kitamura, F., Semba, T., Yasuda-Yoshihara, N., Yamada, K., Nishimura, A., Yamasaki, J., Nagano, O., Yasuda, T., Yonemura, A., Tong, Y., Wang, H., Akiyama, T., Matsumura, K., Uemura, N., Itoyama, R., Bu, L., Fu, L., Hu, X., Wei, F., Mima, K., … Ishimoto, T. (2023). Cancer-associated fibroblasts reuse cancer-derived lactate to maintain a fibrotic and immunosuppressive microenvironment in pancreatic cancer. *JCI insight*, *8*(20), e163022. https://doi.org/10.1172/jci.insight.163022

Koppenol, W. H., Bounds, P. L., & Dang, C. V. (2011). Otto Warburg's contributions to current concepts of cancer metabolism. *Nature Reviews. Cancer*, *11*(5), 325–337. https://doi.org/10.1038/nrc3038

Lee, Y. J., Shin, K. J., Park, S. A., Park, K. S., Park, S., Heo, K., Seo, Y. K., Noh, D. Y., Ryu, S. H., & Suh, P. G. (2016). G-protein-coupled receptor 81 promotes a malignant phenotype in breast cancer through angiogenic factor secretion. *Oncotarget*, *7*(43), 70898–70911. https://doi.org/10.18632/oncotarget.12286

Liberti, M. V., & Locasale, J. W. (2016). The Warburg Effect: How Does it Benefit Cancer Cells?. *Trends in Biochemical Sciences*, *41*(3), 211–218. https://doi.org/10.1016/j.tibs.2015.12.001

Longhitano, L., Vicario, N., Tibullo, D., Giallongo, C., Broggi, G., Caltabiano, R., Barbagallo, G. M. V., Altieri, R., Baghini, M., Di Rosa, M., Parenti, R., Giordano, A., Mione, M. C., & Li Volti, G. (2022). Lactate Induces the Expression of MCT1 and HCAR1 to Promote Tumor Growth and Progression in Glioblastoma. *Frontiers in Oncology*, *12*, 871798. https://doi.org/10.3389/fonc.2022.871798

Pandkar, M. R., Sinha, S., Samaiya, A., & Shukla, S. (2023). Oncometabolite lactate enhances breast cancer progression by orchestrating histone lactylation-dependent c-Myc expression. *Translational Oncology*, *37*, 101758. https://doi.org/10.1016/j.tranon.2023.101758

Pérez-Tomás, R., & Pérez-Guillén, I. (2020). Lactate in the Tumor Microenvironment: An Essential Molecule in Cancer Progression and Treatment. *Cancers*, *12*(11), 3244. https://doi.org/10.3390/cancers12113244

Philp, A., Macdonald, A. L., & Watt, P. W. (2005). Lactate--a signal coordinating cell and systemic function. *The Journal of Experimental Biology*, *208*(Pt 24), 4561–4575. https://doi.org/10.1242/jeb.01961

Polański, R., Hodgkinson, C. L., Fusi, A., Nonaka, D., Priest, L., Kelly, P., Trapani, F., Bishop, P. W., White, A., Critchlow, S. E., Smith, P. D., Blackhall, F., Dive, C., & Morrow, C. J. (2014). Activity of the monocarboxylate transporter 1 inhibitor AZD3965 in small cell lung cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research*, *20*(4), 926–937. https://doi.org/10.1158/1078-0432.CCR-13-2270

Qian, Y., Galan-Cobo, A., Guijarro, I., Dang, M., Molkentine, D., Poteete, A., Zhang, F., Wang, Q., Wang, J., Parra, E., Panda, A., Fang, J., Skoulidis, F., Wistuba, I. I., Verma, S., Merghoub, T., Wolchok, J. D., Wong, K. K., DeBerardinis, R. J., Minna, J. D., … Heymach, J. V. (2023). MCT4-dependent lactate secretion suppresses antitumor immunity in LKB1-deficient lung adenocarcinoma. *Cancer cell*, *41*(7), 1363–1380.e7. https://doi.org/10.1016/j.ccell.2023.05.015

Rao, Y., Gammon, S. T., Sutton, M. N., Zacharias, N. M., Bhattacharya, P., & Piwnica-Worms, D. (2021). Excess exogenous pyruvate inhibits lactate dehydrogenase activity in live cells in an MCT1-dependent manner. *The Journal of Biological Chemistry*, *297*(1), 100775. https://doi.org/10.1016/j.jbc.2021.100775

Rattigan, Y. I., Patel, B. B., Ackerstaff, E., Sukenick, G., Koutcher, J. A., Glod, J. W., & Banerjee, D. (2012). Lactate is a mediator of metabolic cooperation between stromal carcinoma associated fibroblasts and glycolytic tumor cells in the tumor microenvironment. *Experimental Cell Research*, *318*(4), 326–335. https://doi.org/10.1016/j.yexcr.2011.11.014

Rogatzki, M. J., Ferguson, B. S., Goodwin, M. L., & Gladden, L. B. (2015). Lactate is always the end product of glycolysis. *Frontiers in Neuroscience*, *9*, 22. https://doi.org/10.3389/fnins.2015.00022

Sahai, E., Astsaturov, I., Cukierman, E., DeNardo, D. G., Egeblad, M., Evans, R. M., Fearon, D., Greten, F. R., Hingorani, S. R., Hunter, T., Hynes, R. O., Jain, R. K., Janowitz, T., Jorgensen, C., Kimmelman, A. C., Kolonin, M. G., Maki, R. G., Powers, R. S., Puré, E., Ramirez, D. C., … Werb, Z. (2020). A framework for advancing our understanding of cancer-associated fibroblasts. *Nature Reviews. Cancer*, *20*(3), 174–186. https://doi.org/10.1038/s41568-019-0238-1

Wang, T., Ye, Z., Li, Z., Jing, D. S., Fan, G. X., Liu, M. Q., Zhuo, Q. F., Ji, S. R., Yu, X. J., Xu, X. W., & Qin, Y. (2023). Lactate-induced protein lactylation: A bridge between epigenetics and metabolic reprogramming in cancer. *Cell proliferation*, *56*(10), e13478. https://doi.org/10.1111/cpr.13478

Warburg, O., Wind, F., & Negelein, E. (1927). THE METABOLISM OF TUMORS IN THE BODY. *The Journal of General Physiology*, *8*(6), 519–530. https://doi.org/10.1085/jgp.8.6.519

Yao, Y., Bade, R., Li, G., Zhang, A., Zhao, H., Fan, L., Zhu, R., & Yuan, J. (2023). Global-scale profiling of differential expressed lysine-lactylated proteins in the cerebral endothelium of cerebral ischemia-reperfusion injury rats. Cellular and Molecular Neurobiology, 43(5), 1989–2004. https://doi.org/10.1007/s10571-022-01277-6

Ždralević, M., Brand, A., Di Ianni, L., Dettmer, K., Reinders, J., Singer, K., Peter, K., Schnell, A., Bruss, C., Decking, S. M., Koehl, G., Felipe-Abrio, B., Durivault, J., Bayer, P., Evangelista, M., O'Brien, T., Oefner, P. J., Renner, K., Pouysségur, J., & Kreutz, M. (2018). Double genetic disruption of lactate dehydrogenases A and B is required to ablate the "Warburg effect" restricting tumor growth to oxidative metabolism. *The Journal of Biological Chemistry*, *293*(41), 15947–15961. https://doi.org/10.1074/jbc.RA118.004180

Zhang, D., Tang, Z., Huang, H., Zhou, G., Cui, C., Weng, Y., Liu, W., Kim, S., Lee, S., Perez-Neut, M., Ding, J., Czyz, D., Hu, R., Ye, Z., He, M., Zheng, Y. G., Shuman, H. A., Dai, L., Ren, B., Roeder, R. G., … Zhao, Y. (2019). Metabolic regulation of gene expression by histone lactylation. *Nature*, *574*(7779), 575–580. https://doi.org/10.1038/s41586-019-1678-1