

Review

Lactate signalling, exercise and neuroenergetic resilience in cancer supportive care: implications for fatigue, cognition, survivorship and lactylation

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Abstract: Cancer-related fatigue, cancer-related cognitive impairment, psychological distress, sleep disturbance, pain and reduced stress resilience are common and disabling problems across the cancer trajectory. These outcomes are central to psycho-oncology and supportive care, yet their biological links with exercise adaptation remain incompletely understood. Lactate is increasingly recognised as a context-dependent metabolite and signalling molecule rather than a passive end-product of glycolysis. In tumours, persistent lactate accumulation within hypoxic and acidic microenvironments is supported by established evidence linking lactate biology to metabolic symbiosis, immune suppression, angiogenesis, stromal remodelling and therapy resistance. In contrast, exercise-derived lactate is typically transient, systemic and coupled to recovery processes, mitochondrial adaptation, vascular regulation, inflammatory recalibration and inter-organ communication. Evidence from non-cancer exercise and neurobiology models suggests that lactate can influence brain energy metabolism and neuroplasticity through monocarboxylate transporters, HCAR1/GPR81 signalling, BDNF-related pathways, VEGF-mediated vascular responses and lactylation. These mechanisms are potentially relevant to cancer-related fatigue, cognitive impairment, stress resilience and survivorship outcomes, but direct causal evidence in cancer populations remains limited. This narrative review integrates evidence from cancer metabolism, exercise oncology, neuroenergetics, psychoneuroimmunology and lactylation biology to propose a testable lactate stress-adaptation framework for cancer supportive care. We distinguish established tumour-lactate mechanisms, indirect evidence from non-cancer exercise and neural models, and hypotheses that require prospective testing in cancer populations.

Keywords: lactate; cancer supportive care; psycho-oncology; exercise oncology; cancer-related fatigue; cancer-related cognitive impairment; neuroenergetics; survivorship

1. Introduction

Cancer is increasingly recognised not only as a cell-autonomous genetic disease but also as a systemic stress disorder that reshapes host metabolism, immunity, neuroendocrine signalling and tissue energy homeostasis. Cancer patients face ongoing biological stressors such as tumour metabolic demands, chronic inflammation, hypoxia, pain, disrupted sleep, nutritional deficiencies, treatment-related tissue injury and psychosocial adversity [1–5]. Clinically, these stressors appear as cancer-related fatigue, cognitive decline, sleep disturbances, distress, and lowered treatment tolerance, but their biological foundation goes beyond

psychological aspects to include inflammation, mitochondrial and neuroenergetic dysfunction [2,4,6]. Stress, both psychosocial and physiological, can trigger the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system, which in turn can modify immune function and inflammation, impacting tumour progression and survival outcomes [1,3].

At the crossroads of these stress pathways is lactate. Once thought of primarily as a glycolytic byproduct, it is now seen as a mobile carbon source, a redox regulator, a shuttle metabolite between cells, and a signalling molecule [7,8]. High glycolytic activity and lactate accumulation are traditional results of metabolic reprogramming in cancer, but lactate also has functions beyond waste management: it has the ability to power the tricarboxylic acid cycle in tumours, promote metabolic collaboration between oxygen-deprived and oxygenated tumour regions, acidify the tumour microenvironment, and impact immune, stromal, and endothelial sections [9–12]. These observations have shifted tumour lactate from a passive biomarker of anaerobic metabolism to an active mediator of malignant adaptation, immune suppression and therapy resistance [10–13].

This disease-associated lactate biology contrasts sharply with lactate generated during physical exercise. As a controlled metabolic stressor, exercise temporarily boosts circulating lactate and simultaneously enhances cardiorespiratory fitness, muscle function, inflammation management, and quality of life for many cancer survivors [14,15]. Lactate produced by contracting skeletal muscle has been proposed as a myokine or exerkine, with autocrine, paracrine and endocrine-like functions [8,16]. In contrast to the continuous lactate from tumours, lactate produced by exercise is often pulsatile, systemic, and swiftly removed, implying that the behaviour of lactate could signal whether the stress response is beneficial or detrimental [8,16].

The brain is a particularly relevant target of this lactate stress-adaptation axis. Neurons, astrocytes, endothelial cells, and glia work together in a coordinated manner for brain energy metabolism, with lactate being an essential substrate and signal in this system [17,18]. The astrocyte–neuron lactate shuttle hypothesis and related experimental evidence suggest that lactate transport can support neuronal activity, synaptic plasticity and memory formation [17–19]. Lactate signalling from exercise has been associated with brain vascular changes via HCAR1/GPR81-dependent VEGF induction and angiogenesis, as well as with learning and memory pathways linked to hippocampal BDNF [20,21]. These mechanisms are potentially relevant to cancer because cancer and its therapies are associated with fatigue, cognitive decline, neuroinflammation, mitochondrial dysfunction and altered cytokine responses in the brain [4,6].

Lactylation adds another layer of mechanism. The identification of histone lysine lactylation revealed lactate as a substrate for epigenetic control, connecting metabolic conditions to gene expression [22]. Further investigations and reviews have broadened the focus from histones to encompass lysine lactylation of non-histone proteins, suggesting a role for lactylation in cancer metabolism, immune regulation, tumour microenvironment remodelling, and therapeutic resistance [12,13,23,24]. In the nervous system, current research shows that engaging in physical exercise can modify cortical synaptic protein lactylation and boost stress resilience, establishing a direct connection between lactate from exercise, brain protein alterations, and adaptive stress mechanisms [25].

These lines of evidence support a central but still under-tested hypothesis: lactate may function as a context-dependent stress-adaptation signal relevant to

tumour biology and, potentially, to psycho-oncology and cancer supportive care. Tumour-derived lactate may reinforce maladaptive stress responses by facilitating metabolic plasticity, immune suppression and treatment resistance, whereas transient exercise-induced lactate may contribute to host resilience through systemic metabolic signalling, neuroenergetic support, lactate transport, receptor activation and adaptive lactylation [8,14–16,22,25]. This review therefore proposes the lactate stress-adaptation axis as a patient-centred framework linking tumour metabolism with exercise oncology, psychoneuroimmunology, neuroenergetics and survivorship. The purpose is not to define lactate as either harmful or beneficial, but to examine how lactate dynamics may help explain clinically relevant outcomes such as cancer-related fatigue, cancer-related cognitive impairment, stress resilience, treatment tolerance and long-term survivorship [1–4,6,14,15].

To avoid overstating the current evidence, this review separates three levels of inference. First, established evidence supports a role for tumour-associated lactate in metabolic symbiosis, extracellular acidosis, immune suppression, stromal remodelling and selected forms of therapy resistance. Second, indirect evidence from non-cancer exercise and neurobiology models suggests that transient lactate pulses can influence brain substrate use, neurovascular signalling, BDNF-related plasticity and lactylation. Third, whether exercise-derived lactate causally mediates improvements in cancer-related fatigue, cognitive impairment, distress, pain, sleep, treatment tolerance or survivorship outcomes remains a testable hypothesis that requires cancer-specific mechanistic and clinical studies.

2. Methods

This review was designed as a narrative and conceptual synthesis rather than a systematic review or meta-analysis. The aim was to integrate mechanistic and translational evidence from cancer metabolism, exercise physiology, neuroenergetics, psychoneuroimmunology and lactylation biology, and to develop a context-dependent framework for lactate signalling in cancer supportive care.

Literature searches were conducted in PubMed, Web of Science Core Collection and Google Scholar. Searches covered the period from database inception to 10 June 2026. Search terms were grouped into five domains: lactate and cancer metabolism; lactate and exercise; lactate and brain energy metabolism; lactylation biology; and patient-centred supportive care outcomes. The full search strategy is provided in **Supplementary Table 1**.

Eligible sources included peer-reviewed original studies, mechanistic studies, animal and cell models, translational cancer studies, human exercise studies, clinical guidelines, consensus statements and authoritative reviews. Studies were prioritized when they addressed one or more of the following topics: lactate metabolism or signalling in cancer; tumour microenvironment remodelling; exercise-induced lactate responses; monocarboxylate transporter or HCAR1/GPR81 signalling; lactate-related brain energy metabolism or neuroplasticity; cancer-related fatigue or cognitive impairment; lactylation of histone or non-histone proteins; immune suppression; DNA repair; therapy resistance; or survivorship outcomes relevant to psycho-oncology and supportive care.

Exclusion criteria were: non-peer-reviewed sources, studies focused only on athletic performance without mechanistic or clinical relevance to cancer supportive care, papers not addressing lactate, lactylation, exercise adaptation, neuroenergetics or cancer-related symptoms, and studies for which the mechanistic or clinical relevance

to the proposed framework was unclear. Reference lists of key articles were also screened to identify additional relevant studies.

Screening and selection were performed qualitatively. Titles and abstracts were first screened for relevance to the five domains above, followed by full-text review of studies considered central to the framework. Evidence was prioritized in the following order: human cancer or survivorship evidence; tumour-bearing animal models; patient-derived tumour or immune models; mechanistic cell studies; human non-cancer exercise or neurobiology studies; non-cancer animal models; and review or consensus literature. Because this was not a systematic review, no quantitative synthesis or risk-of-bias scoring was performed. However, the strength of evidence was explicitly graded in the evidence tables according to cancer-specificity, consistency across models, and availability of causal perturbation evidence. Box 1 shows Key mechanistic distinctions used in this review.

Box 1. Key mechanistic distinctions used in this review

Lactate versus lactic acid/low pH. Lactate refers primarily to the lactate anion that can function as a carbon substrate, redox-linked metabolite, transporter substrate, receptor ligand and lactylation precursor. Lactic acid and low pH refer to acid stress. In tumours, lactate accumulation and proton export often coexist, but lactate-specific signalling should not be conflated with extracellular acidosis.

Tumour-derived lactate. This refers to lactate generated or accumulated within tumour and stromal compartments, often under chronic glycolytic, hypoxic and acidic microenvironmental stress.

Exercise-derived circulating lactate. This refers to the transient systemic rise in blood lactate during and after exercise, shaped by exercise intensity, recruited muscle mass, baseline fitness, mitochondrial capacity, anaemia, cachexia, treatment exposure and clearance kinetics.

Brain lactate. Central nervous system lactate may be locally produced, transported across cellular compartments or taken up from the circulation. Tumour lactate, systemic blood lactate and brain lactate are not interchangeable measures.

Acute lactate production versus clearance. Peak lactate reflects acute production relative to utilisation, whereas post-exercise clearance reflects oxidation, gluconeogenesis, tissue uptake and recovery capacity.

MCT1/MCT2/MCT4. Monocarboxylate transporters regulate lactate flux. MCT1 is commonly involved in lactate uptake or bidirectional transport, MCT2 is enriched in high-affinity neuronal lactate uptake, and MCT4 is commonly associated with lactate export from glycolytic cells, including some tumour or glial compartments.

HCAR1/GPR81 signalling. HCAR1, also known as GPR81, is a lactate-responsive G-protein-coupled receptor. Receptor-mediated signalling should be distinguished from lactate oxidation or lactate transport.

Histone versus non-histone lactylation. Histone lactylation links lactate availability to chromatin and transcriptional regulation. Non-histone lactylation can modify DNA-repair proteins, metabolic enzymes, immune signalling proteins, mitochondrial proteins or synaptic proteins, and therefore may regulate stress responses through mechanisms beyond transcription.

3. Findings

3.1. Lactate as a context-dependent stress signal in cancer

3.1.1. From metabolic by-product to stress-adaptation molecule

Lactate has undergone a major conceptual redefinition. In the twentieth century,

lactate was largely understood as a glycolytic byproduct that accumulated due to insufficient oxygen or when glycolytic activity outpaced mitochondrial oxidative capacity. This interpretation is now incomplete. Under both aerobic and anaerobic conditions, lactate is constantly produced and consumed, being vital for the body's carbon flow, redox balance, and inter-organ metabolic interactions [7,26]. The lactate shuttle theory reframed lactate as a mobile energy currency that transfers carbon and reducing equivalents between glycolytic and oxidative cells, tissues and organs [7,26]. According to this viewpoint, lactate serves not merely as a marker of metabolic failure but as an active substrate that integrates glycolysis, oxidative phosphorylation, gluconeogenesis, and mitochondrial respiration [7,8,26].

This reinterpretation is especially relevant to cancer. Many tumours display high glycolytic flux and lactate production, but lactate does not merely represent inefficient metabolism. Human lung tumour research has found that lactate can be used as an oxidative fuel, which indicates that the metabolism of lactate in tumours is heterogeneous and can aid in tumour energy production instead of just signalling hypoxia [9]. Experimental work on metabolic symbiosis further demonstrated that tumour cells in hypoxic conditions produce lactate, which can be utilised and oxidised by tumour cells with more oxygen, thus preserving glucose for hypoxic areas and promoting tumour survival in areas with uneven oxygen distribution [27,28]. Therefore, in cancer biology, lactate should be considered both a product of metabolic stress and a substrate for metabolic adaptation [9,27–29].

Lactate serves not only as a carbon source but also as a signalling molecule. It communicates through HCAR1/GPR81, a receptor coupled with G-proteins, originally discovered in adipocytes as a receptor that responds to lactate and reduces lipolysis [30]. HCAR1/GPR81 is now recognised as relevant in multiple tissues, including brain and cancer-associated compartments [31,32]. In tumours, Cancer cell survival, tumour growth, angiogenesis, and immune evasion can be facilitated by lactate–GPR81 signalling, which also affects antigen-presenting cells in the tumour microenvironment through paracrine mechanisms [31]. In the brain, HCAR1/GPR81 has been detected in regions relevant to synaptic regulation and neurovascular coupling, supporting the idea that lactate can function as a neurometabolic signal rather than only a fuel [20,32].

Lactate is also an epigenetic substrate. The identification of histone lysine lactylation established a direct route through which lactate availability can influence gene expression [22]. This finding broadened the biological significance of lactate, extending its role from metabolism and receptor signalling to chromatin regulation. Later studies and reviews centred on cancer have associated lactate and lactylation with immune suppression, tumour microenvironment remodelling and therapy resistance [12,13,23,24]. Current research shows that exercise can modulate lactylation of cortical synaptic proteins and boost stress resilience, implying that lactylation could be involved in the nervous system's adaptive responses to stress [25]. Thus, lactate now needs to be understood as a stress-adaptation molecule with at least four linked identities: energy substrate, intercellular shuttle, receptor ligand and epigenetic substrate [7,8,22,25,33,34].

3.1.2 Cancer as a chronic maladaptive stress state

Cancer imposes chronic biological stress on the host. Stress related to tumours involves more than just their growth; it includes inflammation, hypoxia, acidosis, changes in nutrient allocation, pain, sleep disturbances, treatment side effects, cachexia, and neuroendocrine system activation [1–4,35–38]. Chronic psychosocial

and physiological stress can activate the hypothalamic–pituitary–adrenal axis and sympathetic nervous system, leading to sustained exposure to glucocorticoids and catecholamines [1,3,36,37]. Stress pathways have the potential to impact immune surveillance, the degree of inflammation, the formation of new blood vessels, tumour cell invasion, and the environment surrounding the tumour [1,3,36,37]. Therefore, cancer should not be framed only as a local malignant process; it is also a systemic disorder of stress adaptation.

The metabolic burden of cancer further strengthens this view. Tumours vie with host tissues for glucose, amino acids, and lipids, while inflammatory mediators boost resting energy expenditure and modify the metabolism of skeletal muscle, adipose tissue, and the liver [2,38]. Cancer cachexia exemplifies this maladaptive host response: it is characterized by negative energy balance, skeletal muscle wasting, anorexia, systemic inflammation, fatigue and poor treatment tolerance [38]. The fatigue experienced in cancer is significantly connected to energy regulation issues in the host, inflammatory pathways, and mitochondrial damage from treatment, beyond just subjective fatigue [2]. These observations support the idea that many cancer-related symptoms reflect failure of systemic energetic adaptation under chronic disease pressure [2,38].

Due to rapid tumour growth, abnormal blood vessels, and uneven perfusion, the tumour microenvironment is naturally stressful, causing hypoxia, extracellular acidosis, and nutrient gradients [9,27,35]. Hypoxia and acidity suppress antitumour immunity and create selection pressures that favour tumour-cell plasticity, invasion and therapeutic resistance [35,39]. This process relies heavily on lactate, as it leads to extracellular acidification, aids in metabolic exchanges among cell populations, and directly affects immune and stromal compartments [10,11,27,39]. In this setting, lactate is not simply a metabolic readout; it is part of the machinery through which cancer ecosystems adapt to chronic stress.

Cancer treatments introduce additional stress. Chemotherapy, radiotherapy, targeted therapy, and immunotherapy can damage mitochondria, trigger inflammation, and disrupt the balance of energy in tissues [2,4,6]. In the nervous system, these insults are clinically linked to fatigue, cognitive impairment, sleep disturbance and distress [4,6]. In the periphery, treatment can worsen muscle wasting, nutritional compromise and systemic inflammation [2,38]. For many cancer survivors, exercise interventions are suggested because they enhance physical function, alleviate fatigue, and improve quality of life, but the specific molecular mediators of these effects are still not completely identified [14,15]. Due to exercise causing controlled lactate pulses and cancer creating ongoing lactate-rich environments, lactate emerges as a strong candidate mediator, establishing the conceptual framework for a lactate stress-adaptation axis [8,14,15,25].

3.1.3 The lactate paradox: tumour-derived versus exercise-derived lactate

The primary concern is that lactate can facilitate both disease progression and adaptation. In tumours, lactate is frequently generated when glycolysis is persistently active, during hypoxia, in acidic environments, and under microenvironmental stress [9–12,27,35,39]. Tumour-derived lactate can promote metabolic symbiosis, allowing oxidative tumour cells to use lactate as fuel while preserving glucose for hypoxic glycolytic cells [27–29]. Furthermore, it can play a role in immune suppression by affecting effector immune cell function, modifying dendritic cell antigen presentation, fostering regulatory immune phenotypes, and maintaining an acidic microenvironment [10,31,35,39]. By utilising GPR81/HCAR1 and transporter-

dependent mechanisms, tumour lactate could act as a maladaptive stress signal, supporting malignant ecosystems in surviving nutrient shortages, immune responses, and treatment pressures [13,30,31,39].

Exercise-derived lactate has a different biological context. Lactate levels temporarily increase during physical activity based on intensity, muscle engagement, and metabolic adaptability, before decreasing as it is removed or used by the skeletal muscle, heart, brain, liver, and other tissues [8,26,40]. Typically, the lactate signal is pulsatile instead of chronic, affects the entire system rather than being locally confined, and is associated with broader adaptive responses like improved mitochondrial function, vascular regulation, substrate flexibility, and inflammatory balance [8,14,15,34,40]. Lactate produced during exercise has therefore been proposed as a myokine or exerkine that contributes to inter-organ communication [8]. Lactate can affect brain energy metabolism, neurovascular coupling, and plasticity in the nervous system through mechanisms that depend on transport and receptors [17–21,32].

The contrast between tumour-derived and exercise-derived lactate should not be reduced to “bad lactate” versus “good lactate.” A more robust model suggests that lactate's biological impact is influenced by its source, concentration, duration, compartmentalization, pH environment, transporter expression, receptor availability, and the state of the target cell [7,8,10,27,33,39]. Chronic high local lactate within an acidic tumour microenvironment may reinforce immune escape and tumour adaptation [35,39]. Conversely, temporary increases in lactate from exercise might serve as beneficial signals that aid in host adaptation, such as enhancing neuroenergetic resilience and stress resistance [8,25,34,40]. The same molecule can therefore encode opposite biological meanings depending on its temporal and spatial context.

In cancer care, the lactate paradox is especially crucial. A straightforward approach to inhibit all lactate signalling could theoretically affect adaptive exercise responses, brain energy metabolism, or immune regulation, whereas the unexamined endorsement of lactate as advantageous neglects its established function in tumour metabolic adaptation and immune suppression [10,13,27,31,39]. A more precise framework is needed: Lactate from tumours should be examined as a long-term maladaptive stress signal, whereas lactate from exercise should be considered as a potential adaptive signal that could enhance the body's stress resilience through metabolic neuroenergetic and lactylation-dependent mechanisms [8,22,25,32,40]. This distinction forms the conceptual foundation for the proposed lactate stress-adaptation framework in cancer supportive care (**Figure 1**).

Chronic tumour-associated lactate and transient exercise-induced lactate differ in source, exposure duration, concentration, pH context, tissue compartment and cellular targets. Established cancer evidence supports roles for tumour-associated lactate in metabolic symbiosis, extracellular acidosis, immune suppression, stromal remodelling, angiogenesis and selected forms of therapy resistance. In contrast, evidence that exercise-derived lactate directly mediates improvements in cancer-related fatigue, cognitive impairment, stress resilience or survivorship outcomes remains limited. The exercise-related arm of the figure therefore represents a hypothesis-generating framework based largely on non-cancer exercise and neurobiology evidence, including lactate transport, HCAR1/GPR81 signalling, BDNF-related plasticity, VEGF-mediated neurovascular responses, mitochondrial adaptation and potentially reversible lactylation. Tumour lactate, systemic blood

lactate and brain lactate should not be interpreted as interchangeable measures.

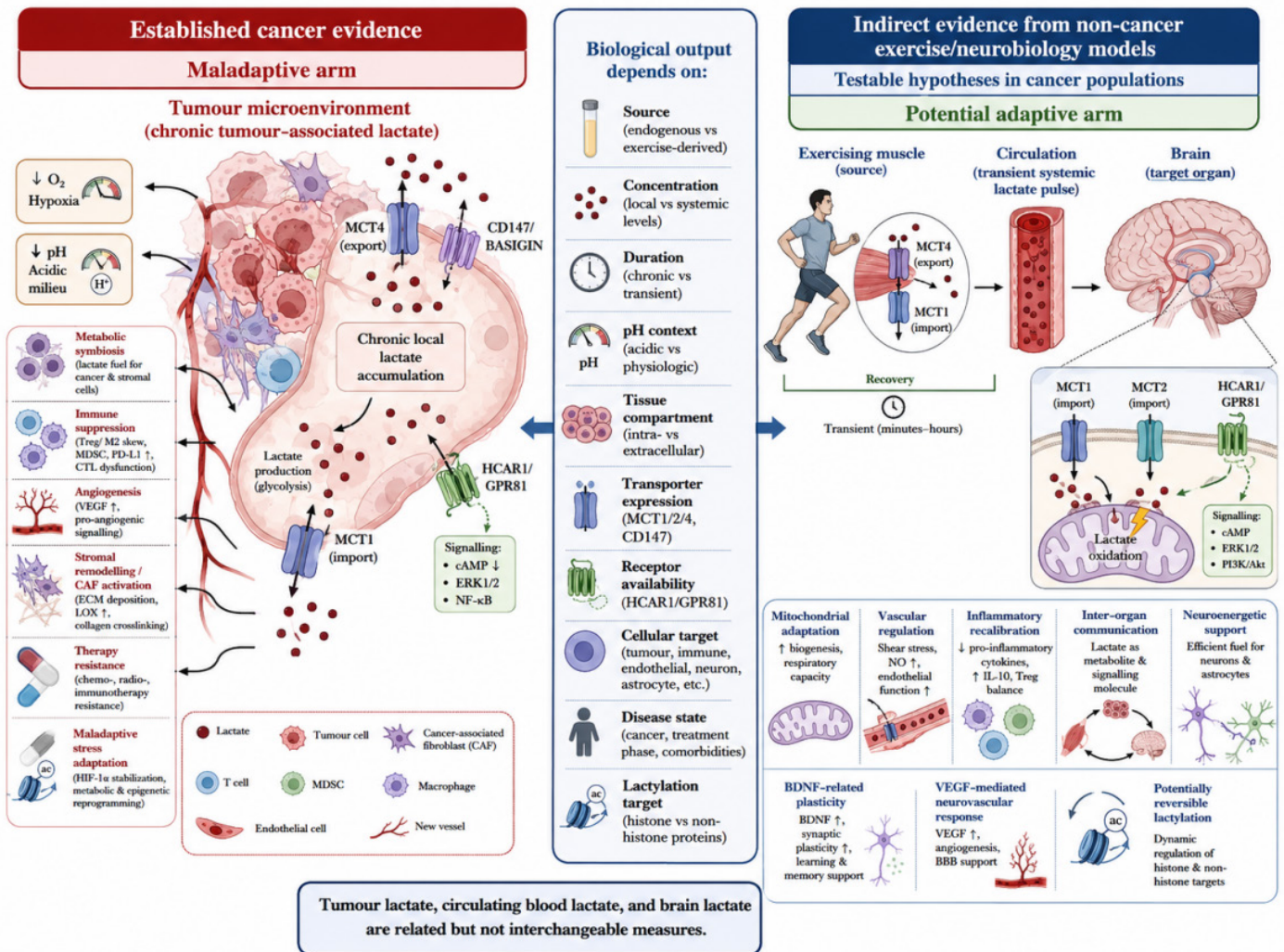


Figure 1. A testable lactate stress-adaptation framework in cancer supportive care.

3.2. Tumour-associated lactate as the maladaptive arm of the proposed framework

3.2.1 Warburg metabolism, lactate accumulation and acidic stress

Aerobic glycolysis is one of the most established metabolic features of malignant cells. In oxygen-rich environments, a significant number of cancer cells prefer to transform glucose-derived pyruvate into lactate rather than fully oxidizing it through mitochondrial respiration [41,42]. Rather than merely being a mitochondrial function defect, this phenotype facilitates quick proliferation by maintaining glycolytic flux, regenerating NAD⁺, supplying biosynthetic intermediates, and enabling tumour cells to cope with changing oxygen availability [41,42]. In this context, lactate production should be interpreted as part of a stress-adaptive metabolic programme rather than as a passive metabolic endpoint.

As a key enzyme, LDHA facilitates the transformation of pyruvate to lactate, supporting NAD⁺ regeneration and allowing glycolysis to occur even when oxygen is scarce, nutrients are limited, or mitochondria are under stress [43]. Reducing LDHA experimentally lowers lactate production and undermines tumour maintenance, suggesting that lactate production plays a direct role in cancer survival rather than

just being a byproduct [43]. Lactate export is equally important. Because intracellular lactate and proton accumulation would impair glycolytic flux and threaten cell viability, cancer cells depend on monocarboxylate transporters, particularly MCT1 and MCT4, along with the chaperone CD147/BASIGIN, to move lactate and protons across the cell membrane [27,44,45]. Disruption of MCT function or CD147-dependent transporter maturation can impair glycolytic tumour energetics, highlighting lactate transport as a metabolic vulnerability [44,45].

The consequence of sustained lactate production and proton export is the formation of an acidic tumour microenvironment. The extracellular environment of solid tumours frequently becomes acidic because fermentative metabolism, poor blood supply, and regional hypoxia work together to generate and trap lactate and H^+ [35,39,42,46]. The biological impact of acidic stress is notable. Gatenby and Gillies argued that the acidity in tumours could provide a selective advantage by supporting acid-resistant tumour phenotypes and damaging surrounding healthy tissues [42]. Experimental imaging studies further showed that tumour invasion can proceed along acidic gradients, supporting the concept that extracellular acidity contributes to local invasion and niche engineering [46]. Therefore, lactate produced by tumours is part of a larger acid-stress mechanism: cancer cells adjust to the acidic environment they generate, whereas immune cells, stromal cells, and nearby normal tissues are functionally hindered by it [35,39,46].

This acid-stress characteristic is crucial to the maladaptive stress adaptation seen in cancer. It enables tumours to sustain glycolytic activity, reallocate metabolic resources, encourage invasion, and inhibit competing host reactions [27,39,42,45,46]. The key point is that lactate is not only a marker of the Warburg effect. It is a functional mediator of the hostile tumour ecosystem.

3.2.2 Lactate-driven tumour microenvironment remodelling

Lactate produced by tumours alters the tumour microenvironment by influencing immune, stromal, and vascular components, with one of its key impacts being the suppression of the immune system. Early experimental work showed that tumour-derived lactic acid suppresses human cytotoxic T-cell proliferation, cytokine production and cytotoxic activity [47]. Subsequent research showed that lactic acid production linked to LDHA hinders the function of both T-cells and NK-cells, thus compromising tumour immunosurveillance [48]. These findings explain why lactate-rich tumours often show poor effector immune activity despite the presence of tumour antigens: elevated lactate levels and reduced pH can form a metabolic obstacle that hinders immune cells from sustaining their glycolytic and effector functions [10,39,47,48].

Macrophages are another major target. Lactic acid from tumours can shift tumour-associated macrophages to a phenotype that supports tumour growth, partly by inducing VEGF and arginase-related pathways through HIF-1 α [49]. In breast cancer models, lactate also induces M2-like macrophage polarisation through ERK/STAT3 signalling [36]. This holds significance as tumour-associated macrophages can facilitate angiogenesis, matrix remodelling, immune suppression, and the dissemination of metastases [11,14,49]. Therefore, lactate does not merely suppress antitumour immunity; it can actively instruct myeloid cells to become components of the tumour-supportive stress niche.

The impact of lactate extends to endothelial cells and the process of angiogenesis. The uptake of lactate via endothelial MCT1 can initiate an NF- κ B/IL-8 pathway, which facilitates tumour angiogenesis [50]. This mechanism is conceptually

important because it shows that lactate can behave as a paracrine signal from tumour cells to non-malignant vascular cells. In this scenario, lactate links the glycolytic process in cancer cells to the remodelling of endothelial cells, thereby aiding tumours in resolving the stress of inadequate perfusion through vascular adaptation [50]. However, the resulting vasculature is often abnormal and inefficient, which can further maintain hypoxia and reinforce lactate production.

Cancer-associated fibroblasts also participate in lactate-based metabolic crosstalk. There is evidence for a lactate shuttle between stromal and epithelial cells in human tumours, where MCT4-positive fibroblasts under oxidative stress export lactate for use by tumour cells, indicating metabolic compartmentalization [51]. Recent studies on lung cancer have demonstrated that lactate from tumours can activate fibroblasts associated with tumours, induce CAF states positive for DESMIN, and promote the recruitment of macrophages through IL-8, thus connecting lactate to stromal activation myeloid recruitment and immune checkpoint resistance [52]. Research shows that lactate can travel in both directions within the tumour environment: tumour cells generate lactate to influence the stroma, and stromal cells can supply lactate to support tumour expansion and invasion [51,52].

Together, these mechanisms place lactate at the centre of tumour microenvironmental remodelling. It suppresses T and NK cells, polarises macrophages, activates fibroblasts, drives angiogenesis and reinforces metabolic symbiosis [27,47–52]. Regarding stress adaptation, this means that lactate produced by tumours helps cancer ecosystems to change hypoxia, nutrient deficiencies, and immune pressure into selective advantages.

3.2.3 Lactylation as a tumour stress-adaptation mechanism

The discovery of lysine lactylation provided a direct molecular mechanism by which lactate can influence gene expression and protein function [22]. In the context of cancer, this is vital because tumour cells commonly accumulate lactate when experiencing hypoxia, elevated glycolytic flux, and therapeutic pressure [12,13,22–24]. Histone lactylation can potentially convert metabolic information into transcriptional programmes that support angiogenesis, immune evasion, proliferation and survival [12,22–24]. Thus, lactylation should be considered more than just a result of lactate buildup; it might function as a molecular memory system that captures prolonged metabolic stress and converts it into adaptive cellular responses.

In hypoxic tumours, histone lactylation is notably important. Hypoxia elevates glycolytic flow and lactate production, which may lead to increased histone lactylation and changes in the expression of genes that respond to stress [12,22,53]. In bladder cancer, hypoxia-induced LDHA activity increased H3K18 lactylation, which activated RBM15 transcription and promoted m6A-dependent stabilization of IGFBP3, thereby enhancing cisplatin resistance [53]. This example highlights the integration of hypoxia, lactate production, histone lactylation, RNA modification, and therapy resistance into a unified stress-adaptation axis.

Non-histone lactylation adds another layer. The strongest current example is NBS1 lactylation. NBS1 is part of the MRN complex, which is critical for DNA double-strand break repair. According to a study, lactate-induced K388 lactylation of NBS1 boosts homologous recombination-mediated DNA repair, assists in MRN complex formation, and is linked to chemotherapy resistance [54]. This finding is highly relevant to the current review because it demonstrates that lactylation can directly regulate the cellular machinery that determines whether cancer cells survive

genotoxic stress.

Lactylation can also reshape the immune tumour microenvironment. Elevated global protein lactylation in pancreatic ductal adenocarcinoma was associated with poor clinical results under immunotherapy; lactate mechanistically induced ENSA-K63 lactylation and triggered STAT3/CCL2 signalling pathways, recruited tumour-associated macrophages and promoted immune checkpoint blockade resistance [55]. This implies that lactylation is active not only within tumour cells but also in the interactions between tumours and immune cells. In essence, lactylation could enable tumours to adjust to metabolic, immune, and therapeutic pressures simultaneously.

Currently, the study of lactylation is still in its early stages, with many unanswered questions about the identity and specificity of lactylation writers, erasers, and readers in various tumour types [12,23,24]. Nevertheless, current evidence supports a defensible working model: in tumours, the persistent accumulation of lactate can drive the lactylation of histone and non-histone proteins, which might stabilize stress-adaptation programmes in cancer cells and their microenvironment [12,13,22–24,53–55].

3.2.4 Lactate, lactylation and therapy resistance

Therapy resistance can be understood as an extreme form of maladaptive stress adaptation. Cancer treatments impose genotoxic, oxidative, metabolic, proteotoxic and immune pressure, and tumour-derived lactate may help malignant cells and their microenvironment withstand these pressures. Lactate metabolism can maintain energy and redox homeostasis, support metabolic flexibility, and reinforce lactate exchange between tumour and stromal compartments [9,27,28,41,43,45,51]. Lactate-rich and acidic tumour environments can also weaken antitumour immunity by suppressing cytotoxic T-cell and NK-cell function and by promoting macrophage- or fibroblast-associated immunosuppressive states [47–49,52]. These mechanisms are particularly relevant to immunotherapy resistance, as elevated lactate and protein lactylation in pancreatic ductal adenocarcinoma have been associated with macrophage accumulation, reduced cytotoxic T-cell infiltration and resistance to immune checkpoint blockade [55].

Lactylation may further support treatment resistance by modifying stress-response machinery. NBS1 lactylation can promote homologous recombination-mediated DNA repair and chemotherapy resistance, while hypoxia-driven H3K18 lactylation in bladder cancer can contribute to cisplatin resistance through RBM15-dependent m6A regulation of IGFBP3 [53,54]. These findings show that lactylation is not merely a marker of lactate accumulation but may alter specific DNA-repair or regulatory pathways that influence treatment response [53,54]. However, proposed links between lactate, lactylation, EMT, stemness, autophagy and drug-tolerant cell states remain less uniformly validated and should be interpreted cautiously [12,13,23,24,46,55].

For a supportive care readership, the main implication is not that lactate should be universally inhibited. Rather, tumour-derived lactate represents the pathological arm of a broader stress-adaptation axis. Its chronic accumulation may support malignant adaptation, whereas transient exercise-induced lactate may participate in host adaptation. This distinction is essential when considering exercise oncology, fatigue management, cognitive symptoms and survivorship, because interventions that indiscriminately suppress lactate biology could theoretically interfere with exercise adaptation, brain energy metabolism or immune recovery [7,8,14,15,17,25].

Table 1. Outlines evidence summary for tumour-associated lactate and lactylation.

Domain	Evidence level	Cancer-specific evidence	Causal evidence	Main translational gap
Metabolic symbiosis	Strong	Strong	Moderate–strong	Spatial mapping of lactate production, uptake and oxidation in patient tumours.
Acidic microenvironment	Strong	Strong	Strong	Integrated measurement of lactate, pH, perfusion, MCT expression and immune state.
Immune suppression	Strong	Strong	Strong	Separation of lactate-specific, low-pH and receptor-mediated effects.
Macrophage polarisation	Moderate–strong	Strong	Moderate	Validation across tumour types and macrophage states.
Angiogenesis	Moderate–strong	Moderate–strong	Moderate	Distinguishing tumour-promoting from physiological vascular adaptation.
CAF/stromal remodelling	Moderate	Moderate	Moderate	Causal links between lactate-conditioned CAF states and therapy resistance.
Histone lactylation	Emerging	Moderate	Moderate	Site-specific validation beyond pan-Kla or global histone signals.
Non-histone lactylation/DNA repair	Emerging but mechanistically strong	Strong in selected models	Strong in selected models	Confirmation across cancer types and clinical treatment-response datasets.
Immunotherapy resistance	Emerging	Moderate	Moderate in selected models	Prospective clinical correlation with lactate/lactylation signatures.

Note: Evidence levels were assigned qualitatively. Strong indicates consistent evidence across multiple models or human cancer datasets with supportive causal perturbation evidence. Moderate indicates biologically coherent evidence with some cancer-specific data but incomplete causal or clinical validation. Weak indicates limited or mainly indirect evidence. Emerging indicates a newly developing mechanism supported by selected studies but not yet broadly replicated. Cancer-specific evidence refers to evidence from cancer patients, tumour tissues, tumour-bearing models or treatment-related cancer models. Causal evidence refers to studies using genetic, pharmacological, transporter/receptor blockade, site-specific mutation, rescue experiments or comparable perturbation approaches.

3.3. Exercise-derived lactate, neuroenergetic resilience and supportive care outcomes: indirect evidence and testable hypotheses

3.3.1 Exercise as controlled metabolic stress

Physical exercise is a controlled and dose-dependent physiological stressor. Whole-body homeostasis is challenged by acute exercise through heightened ATP turnover, substrate flux, oxygen uptake, redox pressure, vascular needs, and immune cell trafficking [56,57]. These perturbations are not pathological when appropriately dosed; rather, they serve as the catalyst for adaptation. Consistent exercise leads to the creation of new mitochondria, better oxidative capacity, increased metabolic flexibility, vascular changes, and anti-inflammatory adjustments in various tissues [56–59]. In this sense, exercise is best understood as a hormetic stressor: it transiently disrupts homeostasis to increase future adaptive capacity.

Lactate is one of the most sensitive metabolic outputs of this controlled stress response. Exercise causes skeletal muscles to contract, which boosts glycolysis

and results in lactate formation, even under aerobic conditions, especially when the glycolytic flow is greater than the local pyruvate oxidation [7,8,26]. Lactate is more than just a byproduct of fatigue; it is quickly transferred between muscle fibers, the heart, liver, brain, and other tissues, where it can be used for oxidation, gluconeogenesis, or signalling [7,8,26]. The magnitude and duration of the lactate pulse depend on exercise intensity, muscle mass recruited, training status, mitochondrial capacity and lactate clearance kinetics [8,26,40].

This difference is crucial in the context of cancer. Unlike lactate from tumours, which tends to build up over time in low-oxygen and acidic environments, lactate produced from exercise is usually temporary, affects the whole body, and is linked to recovery processes [8,40]. Exercise oncology guidelines already support physical activity as a safe and effective intervention for improving fatigue, physical function and quality of life in many cancer survivors [14,15,60]. These clinical suggestions, however, continue to be mostly based on outcomes. The molecular agents that translate exercise stress into host resilience relevant to cancer are still not completely identified. Lactate is a plausible mediator because it links exercise intensity, substrate metabolism, mitochondrial adaptation, inter-organ communication and brain function [8,16,25,59].

Beyond affecting lactate levels, exercise alters systemic biology related to cancer. Contracting skeletal muscles release myokines, extracellular vesicles, and metabolites, which have an impact on the immune, metabolic, and vascular systems [16,58,61]. In tumour-bearing mouse models, voluntary running suppresses tumour growth partly through epinephrine- and IL-6-dependent mobilization and redistribution of NK cells [62]. Reviews of the exercise-regulated tumour microenvironment indicate that physical activity can modify perfusion, immune cell infiltration, inflammation, and metabolic stress in tumours [63,64]. These observations matter because they position exercise not as a generic lifestyle intervention, but as a systemic biological perturbation that can reshape host–tumour interactions [62–64].

3.3.2 Lactate as an exercise-derived systemic signal

Skeletal muscle is a major source of circulating lactate during exercise. During energetic demand, lactate from contracting muscles can be utilised by oxidative muscle fibers, the heart, liver, and brain, facilitating substrate redistribution [7,8,26]. The concept of lactate as an exerkine extends this role beyond fuel metabolism: exercise-derived lactate may act as a circulating signal that coordinates systemic adaptation [8,16]. Multi-omic studies of acute exercise show that physical activity swiftly impacts plasma metabolites, immune pathways, lipid species, and proteins, reinforcing the concept that exercise induces a comprehensive systemic molecular response rather than merely a muscle-specific event [59].

The process of lactate signalling is partly dependent on transport. Monocarboxylate transporters manage the flow of lactate across cell membranes, deciding if lactate acts on a local or systemic level [27,65,66]. In the brain, in endothelial cells and astrocytes, MCT1 is expressed, MCT4 is mainly associated with the export of lactate by astrocytes, and MCT2 is enriched in neurons, supporting the transfer of lactate from glial and vascular compartments to neurons [65–67]. Exercise can also regulate MCT expression in a brain-region-specific manner. A single long treadmill exercise session in rats boosted MCT isoforms, GLUT1, and cytochrome-c oxidase IV in certain brain regions, suggesting that exercise can change the brain's capacity for lactate transport and oxidation [68].

Through HCAR1/GPR81, lactate can also send signals. GPR81 was initially

recognised as a receptor for lactate in fat cells, where it functions to suppress the breakdown of fats [30]. Subsequent work demonstrated HCAR1/GPR81 expression and action in the brain, and exercise-induced lactate has been linked to cerebral VEGF induction and angiogenesis through HCAR1-dependent pathways [20,32]. This mechanism, mediated by receptors, is vital because it enables lactate to act beyond being a carbon source; it can also serve as a ligand that communicates peripheral metabolic stress to vascular, neuronal, and glial structures [20,32].

The systemic signalling role of lactate from exercise in cancer is largely unexplored. Most studies in exercise oncology prioritize clinical outcomes over examining lactate kinetics, MCT expression, HCAR1 activity, or lactate-related brain signalling [14,15,60]. This is a major evidence gap. To confirm lactate's role as a mechanistic mediator of exercise-induced resilience in cancer, upcoming studies must evaluate both acute and chronic lactate responses, separate lactate production from its clearance, and merge these insights with neurocognitive information, inflammatory, mitochondrial and treatment-tolerance endpoints.

3.3.3 Neuroenergetic regulation by lactate

The brain has high metabolic demands and is extremely sensitive to energy stress. Although glucose is the primary fuel circulating under typical conditions, lactate is becoming more acknowledged as a significant substrate and signal within the central nervous system [17,67,69]. According to the astrocyte–neuron lactate shuttle hypothesis, the uptake of glutamate by astrocytes promotes aerobic glycolysis and lactate production, which connects neuronal activity with the release of lactate from astrocytes and its use by neurons [67]. This model remains debated in some details, but extensive experimental work supports a role for lactate transport in neuronal activity, memory and brain energy homeostasis [17,19,69,70].

Neuronal energy metabolism can be directly supported by lactate. Research in living subjects has indicated that lactate can uphold neuronal activity when glucose is scarce and can be oxidised by the brain in a manner dependent on activity [70]. Astrocyte–neuron lactate transport is also required for long-term memory formation in experimental models, suggesting that lactate availability is not merely permissive for neuronal survival but can be necessary for higher-order neural function [19]. The findings are directly applicable to neuroenergetic stress linked to cancer, since fatigue and cognitive decline could partly reflect a compromised ability to fulfill dynamic energy requirements in neural networks [2,4,6,71–73]. Neuronal plasticity is also regulated by lactate. In both cultured neurons and the mouse cortex, L-lactate increases the expression of genes associated with plasticity, including *Arc*, *c-Fos*, and *Zif268*, partly by enhancing NMDA receptor signalling and the ERK pathway [74,75]. Exercise-induced lactate has been linked to learning and memory through SIRT1-dependent activation of hippocampal BDNF [21]. Other reviews have pointed out lactate and BDNF as possible mediators that connect exercise with neuroplasticity [76]. These findings together indicate that lactate can associate energy demand with transcriptional and synaptic modifications [21,74,76].

The model is further expanded by the receptor-mediated effects of lactate. Signalling through HCAR1/GPR81 can affect brain vascular responses, and lactate receptor activation has been associated with exercise-induced cerebral angiogenesis [20,32]. This is relevant because neuroenergetic resilience depends not only on neuronal metabolism but also on vascular supply, astrocytic support, blood–brain barrier transport and glial inflammatory tone [17,20,32,67]. Lactate produced

from exercise might enhance brain resilience to stress via several interconnected pathways: providing substrates, transporting lactate, modulating redox, signalling through receptors, promoting BDNF-related plasticity, and facilitating protein lactylation [21,25,67,74,76].

Recent evidence showing that exercise affects cortical synaptic protein lactylation to boost stress resilience serves as a significant link for this Review [25]. This study connects exercise-induced lactate with brain protein lactylation and behavioural stress adaptation, suggesting that lactate might leave a molecular signature in synaptic structures [25]. Additionally, exercise has been demonstrated to enhance cognitive impairment and reduce neuroinflammation in mice via histone H3 lactylation in microglia [77]. These studies do not prove that the same mechanisms operate in cancer patients, but they offer a framework that can be tested: lactate produced from exercise might enhance the body's ability to handle stress by altering neuroenergetic and neuroimmune processes through metabolic and lactylation-dependent pathways [25,77].

3.3.4 Cancer-related fatigue, cognitive impairment and neuroenergetic resilience

Cancer-related fatigue and cancer-related cognitive impairment are core problems in psycho-oncology and supportive care. Although they are often assessed as symptoms, they may also reflect impaired host energy regulation under chronic biological and psychosocial stress. Inflammatory signalling, neuroendocrine imbalance, mitochondrial dysfunction, sleep disturbance and altered energy metabolism are associated with fatigue in cancer patients [2,60,71]. Pain should also be included in this clinical framework. Recent population-based survivorship evidence indicates that cumulative adverse childhood experience exposure is associated with cancer-related pain among adult cancer survivors, supporting the need to incorporate early-life adversity, trauma-informed assessment and allostatic-load variables when evaluating stress resilience and patient-reported outcomes [5]. This evidence should be interpreted as survivorship context rather than as evidence that adverse childhood experiences directly alter lactate signalling. Chemotherapy-induced behavioural toxicities, including fatigue and cognitive dysfunction, have also been linked to neuroinflammation, mitochondrial injury and altered tissue bioenergetics [72]. Cancer-related cognitive impairment involves changes in attention, memory, processing speed and executive function, and may arise from direct neurotoxicity, inflammation, vascular changes, hormonal disruption, genetic vulnerability and altered brain network function [4,6,73,78,79]. These mechanisms make neuroenergetic resilience a useful patient-centred concept. In cancer supportive care, resilience should not be restricted to psychological coping. It should also include the capacity of neural, immune, endocrine, vascular and mitochondrial systems to maintain function despite tumour burden, treatment toxicity, inflammation, distress and sleep disruption [1–4,6,71,72]. Exercise is one of the few supportive care interventions that can simultaneously target muscle function, cardiorespiratory fitness, mitochondrial capacity, inflammation, sleep, vascular health and brain plasticity [14,15,56,57,60]. This is why exercise oncology is directly relevant to fatigue, cognition, treatment tolerance and survivorship rather than being merely an adjunct lifestyle recommendation.

Lactate is a plausible, but not yet proven, mediator of these effects. The biological rationale is coherent: exercise generates transient lactate pulses; lactate can be transported into or produced within the brain; lactate can support

neuronal oxidation; lactate can activate HCAR1/GPR81; lactate can induce BDNF-associated plasticity; and lactate can contribute to protein lactylation linked to stress resilience [8,20,21,25,32,67,69,70,74,76]. However, most evidence linking exercise-derived lactate to neuroenergetic resilience comes from non-cancer models [21,25,74,77]. In cancer populations, the evidence is stronger for exercise improving fatigue, physical function and quality of life than for lactate specifically mediating these benefits [14,15,60]. This distinction should be maintained to avoid overstating the clinical evidence.

The most useful formulation for supportive care is therefore not that lactate explains all exercise benefits, but that lactate dynamics may help identify why some patients experience greater improvements in fatigue, cognition or stress resilience than others. Preclinical evidence supports the broader idea that exercise can protect against treatment-associated energetic and inflammatory stress. For example, treadmill exercise improved doxorubicin-induced apoptosis and mitochondrial dysfunction associated with central fatigue [80], and other animal studies suggest that exercise may reduce neuroinflammation and strengthen memory-related signalling after chemotherapy-like injury [72,80]. Future human studies should combine patient-reported fatigue, cognitive testing, sleep and distress measures with lactate kinetics, inflammatory markers, mitochondrial outputs and, where feasible, neuroimaging or magnetic resonance spectroscopy [4,14,15,60,78,79]. Mechanistic cancer models should compare exercise with exogenous lactate, lactate transport blockade, HCAR1 inhibition and lactylation perturbation to test whether exercise-derived lactate is only associated with resilience or actively mediates it [20,25,30,32]. Clinically, future studies should stratify or at least record tumour type, disease stage, treatment phase, treatment modality, baseline fitness, skeletal muscle mass, anaemia, cachexia, pain burden, sleep disturbance, distress, medication use and inflammatory status. These factors may modify both exercise tolerance and lactate kinetics, and therefore should not be treated as background variables only. **Table 2** outlines Patient-centred outcomes and proposed measurement domains for lactate-dynamics studies in cancer supportive care. Because the cancer-specific evidence for exercise-derived lactate, neuroenergetic resilience and supportive-care outcomes is less mature than the evidence for tumour-associated lactate biology, the current evidence base and main translational gaps are summarized separately in **Table 3**.

Table 2. Patient-centred outcomes and proposed measurement domains for lactate-dynamics studies in cancer supportive care.

Outcome domain	Example clinical measures	Biological/exercise-linked measures	Suggested timing	Selected supporting references
Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Brief Fatigue Inventory (BFI), EORTC QLQ-C30 fatigue items	Resting lactate, peak exercise lactate, post-exercise lactate clearance, C-reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor- α (TNF- α), mitochondrial markers	Baseline, acute exercise test, post-exercise recovery, post-intervention	[14,15,60,71]

Continuation Table:

Outcome domain	Example clinical measures	Biological/exercise-linked measures	Suggested timing	Selected supporting references
Cognition	Montreal Cognitive Assessment (MoCA), Trail Making Test, Digit Symbol Substitution Test, Hopkins Verbal Learning Test-Revised, International Cognition and Cancer Task Force (ICCTF)-recommended cognitive batteries	Lactate kinetics, brain-derived neurotrophic factor (BDNF), neuroimaging or magnetic resonance spectroscopy when feasible	Baseline and post-intervention; optional acute testing in mechanistic studies	[4,6,73,78,79]
Sleep	Pittsburgh Sleep Quality Index (PSQI), actigraphy, sleep diary	Post-exercise lactate recovery, inflammatory markers, cortisol rhythm where feasible	Baseline, repeated assessment during intervention, follow-up	[2,4,60,71]
Distress and stress resilience	Distress Thermometer, Hospital Anxiety and Depression Scale (HADS), Perceived Stress Scale, stress-resilience questionnaires where appropriate	Cortisol, catecholamines, inflammatory markers, heart-rate response, perceived exertion	Baseline, acute exercise test, repeated follow-up	[1,3,60,71]
Pain	Brief Pain Inventory (BPI), PROMIS Pain Interference, analgesic use, pain interference with sleep and activity	Inflammatory markers, neuroendocrine markers, medication exposure, trauma-informed history, allostatic-load variables	Baseline and follow-up	[5,38]
Physical function	6-minute walk test, sit-to-stand test, handgrip strength, VO ₂ peak or submaximal exercise testing	Lactate threshold, heart rate, rating of perceived exertion (RPE), workload, oxygen uptake when available	Baseline exercise test and post-training assessment	[14,15,56,57,60]
Treatment tolerance	Dose delays, dose reductions, treatment interruptions, adverse events, hospitalizations, treatment completion	Lactate clearance, inflammatory markers, nutritional status, haematological status, skeletal muscle mass	During treatment cycles and intervention follow-up	[2,14,15,38,60]
Exercise prescription and adherence	Aerobic and/or resistance exercise mode, intensity, duration, frequency, progression, supervision, adherence, adverse exercise events	Lactate threshold, peak lactate, lactate area under the curve (AUC), recovery slope, RPE, heart-rate response	Each acute exercise test and across repeated training adaptation	[14,15,56,57,59,60]

Note: The measures listed are examples of commonly used patient-reported, performance-based or exercise-linked outcomes for cancer supportive care and exercise-oncology studies. The selected supporting references indicate the relevance of each outcome domain to cancer supportive care, exercise oncology, fatigue, cognition, survivorship or lactate-dynamics research; they are not intended as exhaustive validation references for every individual scale. If required by the journal, scale-specific validation references can be added separately.

Abbreviations: AUC, area under the curve; BDNF, brain-derived neurotrophic factor; BFI, Brief Fatigue Inventory; BPI, Brief Pain Inventory; CRP, C-reactive protein; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HADS, Hospital Anxiety and Depression Scale; ICCTF, International Cognition and Cancer Task Force; IL-6, interleukin-6; MoCA, Montreal Cognitive Assessment; PROMIS, Patient-Reported Outcomes Measurement Information System; PSQI, Pittsburgh Sleep Quality Index; RPE, rating of perceived exertion; TNF- α , tumour necrosis factor- α ; VO₂peak, peak oxygen uptake.

Table 3. Evidence summary for exercise-derived lactate and neuroenergetic resilience.

Domain	Evidence level	Cancer-specific evidence	Causal evidence	Main translational gap
Exercise-derived lactate as systemic signal	Moderate	Weak–moderate	Moderate outside cancer	Direct lactate-kinetic studies in cancer patients.
MCT transport and brain energetics	Moderate	Weak	Moderate outside cancer	Linking exercise lactate, MCT expression and fatigue/cognition outcomes.
HCAR1/GPR81 and VEGF signalling	Moderate	Weak	Moderate outside cancer	Cancer-specific neurovascular studies.
BDNF and neuroplasticity	Moderate	Weak	Moderate outside cancer	Direct evidence in cancer-related cognitive impairment.
Exercise and cancer-related fatigue	Strong for exercise benefit; weak for lactate mediation	Strong for exercise benefit	Moderate for exercise; weak for lactate	Trials integrating fatigue outcomes with lactate kinetics.
Exercise and cancer-related cognitive impairment	Weak–moderate	Weak	Weak	Trials combining lactate kinetics, cognitive testing and neuroimaging.
Exercise-induced lactylation and neural resilience	Emerging	Very weak in cancer	Moderate outside cancer	Perturbation studies testing lactylation as mediator.

Note: Evidence-level definitions are the same as those described in **Table 2**. The exercise-related domains should be interpreted as translational hypotheses unless supported by direct cancer-specific evidence.

3.4. Lactylation as a candidate molecular memory of stress and translational target

3.4.1 Histone lactylation and transcriptional stress programmes

Histone lactylation provides a direct biochemical route through which lactate availability can be converted into transcriptional regulation. Histone lysine lactylation was initially discovered to demonstrate that intracellular lactate buildup can boost histone lactylation and change gene expression programmes, notably during macrophage activation and resolution-like responses [22]. This finding changed the interpretation of lactate from a metabolic end-product or signalling ligand into a substrate for chromatin modification. In the framework of cancer stress adaptation,

this is critical: Persistent lactate buildup in tumours might not just indicate glycolytic stress, but could also support transcriptional programmes that enable cancerous and stromal cells to adjust to hypoxia, inflammation, immune challenges, and treatment [12,13,22–24,53–55,81,82].

The control of lactylation by enzymes is still being clarified, with p300/CBP and other acyltransferase-related processes involved in histone lactylation triggered by lactate, and p300-mediated lactylation has been shown experimentally in cellular differentiation models [83]. More recent work has expanded the enzymatic model by showing that lactyl-CoA availability can be generated locally in the nucleus. It has been reported that nuclear GTPSCS functions as a lactyl-CoA synthetase, aiding in histone lactylation and glioma formation, while ACSS2 can also serve as a lactyl-CoA synthetase and collaborate with KAT2A to promote histone lactylation and tumour immune evasion [84,85]. These findings are important because they suggest that the process of histone lactylation is affected by more than just the concentration of lactate; it is also shaped by subcellular lactyl-CoA synthesis, nuclear metabolic enzymes, and writer complexes associated with chromatin [84,85].

Histone lactylation may therefore function as a transcriptional stress programme. Lactylome analysis in hepatocellular carcinoma suggests that lactylation-dependent processes aid in metabolic adaptation, connecting lactate-based modifications to tumour growth and metabolic adaptability [86]. In colorectal cancer, KRAS mutation has been linked to increased H3K9 lactylation, which promotes tumour progression by facilitating cholesterol transporter GRAMD1A expression [87]. Hypoxia-induced LDHA activity in bladder cancer boosts H3K18 lactylation and contributes to cisplatin resistance through the m⁶A regulation of IGFBP3 by RBM15 [53]. Together, these studies support a model in which histone lactylation translates oncogenic metabolism and hypoxic stress into gene-expression programmes that promote growth, survival and treatment resistance [53,86,87].

Histone lactylation may also regulate immune and inflammatory transcriptional states. In macrophages, lactate-driven histone lactylation was first discovered, emerging during the late M1 polarisation phase and triggering genes that are part of homeostatic and reparative pathways [22]. In tumours, however, similar chromatin logic may become maladaptive: lactate-rich microenvironments can drive macrophage polarisation, immune suppression and tumour-supportive inflammation [49,55]. Therefore, histone lactylation should not be seen as inherently promoting or reducing inflammation. Its effects are influenced by the type of cell, timing, length of stress, and the surrounding cytokine and metabolic conditions [22,49,55,81,82].

3.4.2 Non-histone lactylation and cellular stress machinery

Non-histone lactylation broadens the field from chromatin regulation to direct control of cellular machinery. Evidence currently shows that lactylation can happen on metabolic enzymes, mitochondrial proteins, DNA-repair factors, cell cycle regulators, immune signalling proteins, and synaptic proteins [25,54,88–92]. This matters because stress adaptation is not mediated only by transcription. Rapid adjustments in DNA repair, mitochondrial respiration, protein interactions, cytoskeletal dynamics, immune signalling, and synaptic function are also necessary for cells. Non-histone lactylation provides a plausible mechanism for this faster and more direct layer of metabolic regulation.

DNA repair is the strongest current example in cancer. In response to DNA damage, MRE11, a vital component of the MRN complex, becomes lactylated, promoting homologous recombination repair and resistance to chemotherapy. NBS1

lactylation also plays a role in supporting effective DNA repair and chemotherapy resistance [54]. More recently, XLF lactylation has been shown to promote non-homologous end-joining repair and chemoresistance in cancer [93]. Collectively, these studies suggest that lactate in tumours can directly modify DNA-repair machinery, allowing cancer cells to resist genotoxic therapies. This serves as a compelling example of lactylation acting as a molecular memory of stress: treatment causes damage; tumour glycolysis produces lactate; lactylation enhances repair ability; surviving cells become more resilient [54,89,93].

Metabolic enzymes and mitochondrial proteins also undergo lactylation. Under hypoxic conditions, mitochondrial protein lactylation can occur and reduce oxidative phosphorylation, implying that lactylation might aid cells in regulating mitochondrial function when oxygen is scarce [91]. Proteomic analysis in SW480 colon cancer cells identified PFKFB3 lactylation and suggested that lactylation can modulate glycolytic enzyme activity [92]. SIRT3-dependent delactylation of cyclin E2 in hepatocellular carcinoma reduces tumour growth, suggesting that non-histone lactylation plays a role in regulating the cell cycle and that delactylation might be a target for therapy [88]. These studies support a broader model in which lactylation participates in the metabolic rewiring, redox adaptation and proliferative control of cancer cells [88,91,92].

There are additional targets in immune and inflammatory proteins. Lactate can initiate HMGB1 lactylation in macrophages through MCT-dependent uptake and p300/CBP-related pathways, promoting the release of HMGB1 during inflammatory stress [90]. Although this evidence comes mainly from sepsis and inflammatory disease models rather than cancer, it is relevant because tumour-associated macrophages are exposed to high lactate and inflammatory cues simultaneously [49,55,90]. Elevated protein lactylation in pancreatic ductal adenocarcinoma enhances an immunosuppressive microenvironment and therapeutic resistance through macrophage recruitment and STAT3/CCL2 signalling pathways [55]. This supports the possibility that non-histone lactylation in immune cells may help encode whether inflammation resolves, persists or becomes tumour-supportive [55,90].

In the nervous system, non-histone lactylation is emerging as a candidate mechanism of adaptive stress resilience. Engaging in physical exercise can lead to lactylation of cortical synaptic proteins and enhance stress resilience, while the lactylation of histone H3 in microglia due to exercise has been associated with better cognitive function and reduced neuroinflammation in mice [25,77]. These findings are not yet established in cancer patients, but they are central to the present framework. It is suggested that lactylation could facilitate both the adaptation of tumours to malignancy and the host's neuroenergetic adaptation when exercise causes transient lactate production [25,77].

3.4.3 Adaptive versus maladaptive lactylation

A useful way to frame lactylation is to distinguish adaptive from maladaptive stress memory. In adaptive lactylation, the process is transient, reversible, and aids in restoring function after physiological stress. Maladaptive lactylation, however, is chronic, contextually reinforced, and linked to ongoing pathological persistence, such as tumour survival, immune evasion or therapy resistance. By making this distinction, we avoid the simplistic notion that lactylation is purely good or bad. The same biochemical modification can facilitate tissue repair in some situations and contribute to tumour development in others (**Figure 2**) [22,25,55,86,89].

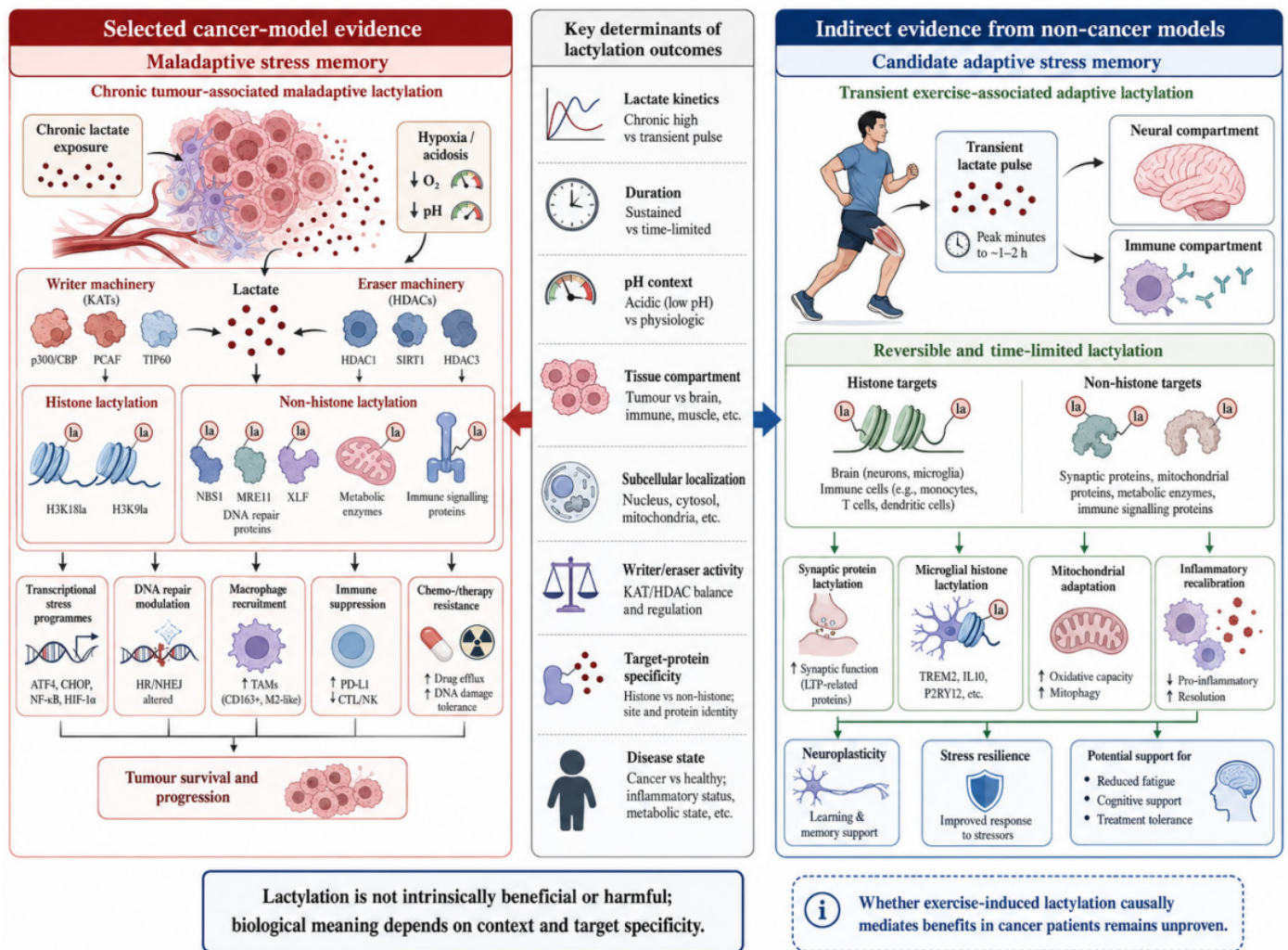


Figure 2. Lactylation as a candidate molecular memory of stress adaptation.

Lactylation may encode divergent stress-response programmes depending on lactate kinetics, cellular context, pH environment, subcellular localization, writer/eraser activity and target-protein specificity. In tumours, chronic glycolytic and hypoxic stress can promote histone and non-histone lactylation, including H3K18la, H3K9la and lactylation of DNA-repair proteins such as NBS1, MRE11 and XLF. These mechanisms have been linked in selected cancer models to transcriptional stress programmes, DNA repair, immune suppression, macrophage recruitment, chemoresistance and tumour survival. In contrast, exercise-induced lactylation in neural or immune compartments is currently supported mainly by non-cancer animal models and should be interpreted as a candidate mechanism of adaptive stress resilience rather than an established mechanism in cancer patients. Whether exercise-induced lactylation causally mediates improvements in cancer-related fatigue, cognition, pain, distress, treatment tolerance or survivorship outcomes remains to be directly tested.

Exercise-induced lactylation provides the clearest model of potentially adaptive lactylation. In mice, a single session of high-intensity interval training can cause protein lactylation that is specific to certain tissues and varies over time, with lactylation levels peaking post-exercise and then gradually returning to baseline [94]. This supports the idea that physiological lactate pulses can generate temporally

constrained lactylation signals rather than permanently altered protein states. In the brain, exercise-induced cortical synaptic protein lactylation has been linked to improved stress resilience [25]. As a result, lactate produced from exercise might lead to a type of lactylation that is rhythmic, compartmentalized, and integral to recovery biology.

Tumour-associated lactylation differs in source and timing. Cancer cells often maintain high glycolytic flux, high lactate output, hypoxia and acidosis over long periods [27,39,41–46]. Chronic lactate exposure can aid in histone and non-histone lactylation programmes that encourage metabolic adaptation, DNA repair, macrophage recruitment, immune suppression, and therapy resistance [53–55,86,87,89,93]. In this setting, lactylation is less likely to represent a transient recovery signal and more likely to become part of a malignant adaptive state. The fundamental principle of the lactate stress-adaptation axis is that intermittent lactate might represent physiological resilience, while persistent tumour lactate could signify pathological adaptation.

However, this model is still a hypothesis and not an established rule, with several uncertainties persisting. Initially, numerous lactylation studies depend on pan-Kla antibodies or enrichment-based proteomics, necessitating meticulous validation of site specificity and functional significance [90,95,96]. Moreover, lactylation can occur at many sites, but only a minority have been causally tested through site-specific mutation, writer/eraser perturbation, or rescue experiments [54,88,89,93]. In addition, lactylation may interact with acetylation, succinylation, crotonylation, phosphorylation and methylation, making it difficult to assign biological effects to one mark in isolation [96–98]. Lactylation may ultimately hold different meanings in tumour cells, macrophages, T cells, astrocytes, microglia, and neurons [22,25,49,55,77].

Therefore, the most defensible formulation is not that exercise-induced lactylation is generally positive, whereas tumour-related lactylation is usually negative. The biological impact of lactylation, however, is determined by factors such as the origin of lactate, duration of exposure, subcellular location, enzyme presence, and the identity of the target protein [22,54,84–86,97–100]. This is precisely why lactylation is an attractive but difficult translational target.

3.4.4 Future directions for psycho-oncology and cancer supportive care

For the lactate–lactylation axis to have translational importance in psycho-oncology and supportive care, future studies must move beyond resting blood lactate and tumour-centred biomarkers alone. Resting lactate is insufficient because it cannot distinguish chronic pathological exposure from transient exercise-induced lactate pulses. Human exercise-oncology studies should assess lactate kinetics, including resting lactate, peak exercise lactate, lactate threshold, post-exercise clearance, lactate area under the curve and changes in these parameters after repeated training. These measurements should be interpreted together with exercise intensity, workload, heart rate, perceived exertion, oxygen uptake when feasible, baseline fitness, skeletal muscle mass, anaemia, cachexia, treatment exposure and recovery capacity [7,8,14,15,26,38,40].

Tumour lactate, systemic blood lactate and brain lactate should be treated as related but distinct compartments. Tumour lactate reflects local metabolic and microenvironmental conditions, including glycolysis, hypoxia, perfusion, pH and stromal-immune interactions. Circulating lactate reflects the balance between systemic production, utilisation and clearance during exercise or illness. Brain lactate reflects local production, transport and uptake across neuronal, glial

and vascular compartments. Peripheral lactate kinetics should therefore not be interpreted as a direct proxy for tumour lactate or central nervous system lactate availability [9,18,19,27,35,39,66,67].

A supportive care-oriented biomarker strategy should include, but not be limited to, lactylation. At least three layers are required. The first layer involves targeted histone lactylation, such as H3K18la, H3K9la and H4K16la, measured in tumour tissues, circulating immune cells or experimental brain regions when feasible. The second layer is global protein lactylation, assessed by pan-Kla immunoblotting, immunoprecipitation or mass spectrometry. The third layer is site-specific functional lactylation, including DNA-repair proteins, metabolic enzymes, immune signalling proteins or synaptic proteins, because only site-specific data can connect lactylation with defined mechanisms. However, lactylation readouts should be interpreted cautiously because pan-Kla signals do not establish site specificity or causal function [22,25,53,54,86,87,89,90,93,95,100].

Clinical studies should integrate patient-centred outcomes with biological measurements. Fatigue, cognition, distress, sleep, pain, treatment tolerance and physical function should be assessed using validated patient-reported or performance-based measures, and these should be aligned with acute exercise lactate sampling and recovery measurements. Pain and stress-history assessment should be incorporated because survivorship symptom burden may be shaped by early-life adversity and allostatic-load pathways. Tumour type, disease stage, treatment phase, treatment modality, baseline cardiorespiratory fitness, muscle mass, anaemia, cachexia, pain, sleep disturbance, distress and medication use should be recorded because each may modify lactate kinetics and exercise tolerance [5].

Causal testing is now the main bottleneck. In preclinical cancer models, exercise should be compared with exogenous lactate, lactate clamps, LDHA modulation, monocarboxylate transporter blockade, HCAR1/GPR81 inhibition and perturbation of lactylation writers or erasers. If blockade of lactate transport or receptor signalling abolishes exercise-induced improvements in fatigue-like behaviour, cognitive performance, inflammatory tone or treatment tolerance, then a stronger causal role for lactate would be supported. If these benefits persist, lactate should be interpreted as an associated marker or one component of a broader exercise response rather than the principal mediator [20,25,27,30,32,84,85,97–100].

Therapeutically, lactate biology should not be approached as a simple “block lactate” or “increase lactate” problem. Selective targeting of chronic tumour-associated lactate production, transport or lactylation-dependent DNA repair may enhance anticancer treatment in selected contexts. However, broad inhibition of lactate pathways could theoretically disrupt exercise adaptation, brain energy metabolism, immune resolution or tissue repair. A rational translational strategy will require cancer-specific testing to determine whether pathological tumour-lactate programmes can be suppressed while physiological exercise-induced lactate responses are preserved [7,8,14,15,26,38,40].

4. Limitations

This Review has several limitations. First, it is a narrative and conceptual synthesis rather than a systematic review or meta-analysis; therefore, the literature selection may be subject to selection bias despite the expanded search strategy and evidence-prioritization criteria. Second, the evidence base is uneven across domains. Tumour-associated lactate mechanisms are supported by stronger cancer-

specific mechanistic evidence than the proposed links between exercise-derived lactate, neuroenergetic resilience, fatigue, cognition and survivorship outcomes. Third, much of the evidence connecting exercise lactate to brain plasticity, HCAR1/GPR81 signalling, BDNF-related pathways and adaptive lactylation comes from non-cancer models. These findings should not be assumed to operate identically in cancer patients. Fourth, lactate, lactic acid/low pH, systemic blood lactate, tumour lactate and brain lactate are biologically distinct and cannot be used interchangeably. Fifth, lactylation biology is still emerging, and many studies rely on global or pan-Kla measurements that do not establish site-specific function. Finally, cancer type, disease stage, treatment phase, anaemia, cachexia, pain, sleep disturbance, distress, medication use and baseline fitness may all modify lactate kinetics and exercise tolerance, but these modifiers have not yet been systematically integrated into cancer exercise-oncology trials.

5. Conclusion

Lactate is not simply a metabolic waste product, but a context-dependent metabolite and signalling molecule linking metabolism, stress adaptation, immune regulation, neuroenergetics and cellular plasticity. In tumours, persistent lactate accumulation within hypoxic and acidic microenvironments is supported by substantial evidence as a contributor to metabolic symbiosis, extracellular acidosis, immune suppression, angiogenesis, stromal remodelling, lactylation-dependent stress programmes and selected forms of therapy resistance. This represents the best-established arm of the proposed framework.

In contrast, the role of exercise-derived lactate in cancer supportive care remains more hypothetical. Exercise-induced lactate is transient, systemic and embedded within broader adaptations involving mitochondrial function, vascular regulation, inflammatory recalibration, inter-organ communication and neuroplasticity. Evidence from non-cancer models suggests that lactate may influence brain energy metabolism, HCAR1/GPR81 signalling, BDNF-related plasticity, VEGF-mediated vascular responses and lactylation. However, whether these mechanisms causally mediate improvements in cancer-related fatigue, cognitive impairment, distress, sleep, pain, treatment tolerance or survivorship outcomes has not yet been established in cancer populations. The central clinical question is therefore not whether lactate is good or bad. The more useful question is whether lactate dynamics can help explain heterogeneity in symptom burden, exercise response and resilience among cancer patients and survivors. Future studies should integrate lactate kinetics, transporter and receptor activity, inflammatory and neuroendocrine markers, mitochondrial function, lactylome profiling, exercise prescription variables and validated patient-reported or performance-based outcomes. A rational translational strategy may ultimately require selective targeting of chronic tumour-associated lactate pathways while preserving physiological lactate responses to exercise; however, this therapeutic distinction requires direct testing in cancer-specific models and prospective exercise-oncology studies.

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Supplementary material

Supplementary Table 1. Narrative review search strategy and evidence-selection framework.

Search domain	Database/ source	Example search string	Screening focus	Evidence prioritization
Lactate and cancer metabolism	PubMed	("lactate" OR "lactic acid") AND ("cancer" OR "tumour" OR "tumor" OR "neoplasm") AND ("metabolism" OR "Warburg effect" OR "glycolysis" OR "metabolic symbiosis" OR "tumour microenvironment" OR "tumor microenvironment")	Studies addressing lactate production, uptake, oxidation, glycolytic reprogramming, metabolic symbiosis, tumour hypoxia or tumour metabolic adaptation.	Human tumour studies and tumour-bearing animal models were prioritized over general cell-line studies; mechanistic studies with perturbation of LDHA, MCTs or related metabolic pathways were prioritized.
Lactate, hypoxia, acidosis and tumour microenvironment	PubMed; Web of Science Core Collection	("lactate" OR "lactic acid") AND ("hypoxia" OR "acidosis" OR "low pH" OR "extracellular pH") AND ("tumour microenvironment" OR "tumor microenvironment" OR "immune suppression" OR "invasion" OR "angiogenesis")	Studies distinguishing lactate-specific effects from low-pH or lactic-acid effects, including extracellular acidosis, invasion, angiogenesis and immune suppression.	Studies directly measuring or manipulating lactate, pH, MCT transport or hypoxia-related pathways were prioritized.
Lactate transport and receptor signalling in cancer	PubMed; Web of Science Core Collection	("lactate" OR "lactic acid") AND ("MCT1" OR "MCT2" OR "MCT4" OR "monocarboxylate transporter" OR "CD147" OR "BASIGIN" OR "HCAR1" OR "GPR81") AND ("cancer" OR "tumour" OR "tumor" OR "immune" OR "angiogenesis" OR "therapy resistance")	Studies addressing lactate transport, receptor-mediated signalling, tumour growth, immune regulation, angiogenesis or treatment response.	Mechanistic studies using transporter inhibition, receptor inhibition, genetic knockdown/knockout or rescue experiments were prioritized.
Lactate and immune suppression	PubMed; Web of Science Core Collection	("lactate" OR "lactic acid") AND ("T cell" OR "NK cell" OR "macrophage" OR "dendritic cell" OR "immune suppression" OR "tumour-associated macrophage" OR "tumor-associated macrophage") AND ("cancer" OR "tumour" OR "tumor")	Studies examining cytotoxic T-cell function, NK-cell function, macrophage polarization, dendritic-cell antigen presentation or immunosuppressive tumour microenvironments.	Cancer-specific immune studies and studies separating lactate effects from acidification effects were prioritized.
Lactate and stromal remodelling	PubMed; Web of Science Core Collection	("lactate" OR "lactic acid") AND ("cancer-associated fibroblast" OR "CAF" OR "stroma" OR "stromal remodelling" OR "extracellular matrix" OR "fibroblast activation") AND ("cancer" OR "tumour" OR "tumor")	Studies addressing lactate-mediated crosstalk between tumour cells, fibroblasts, endothelial cells and immune cells.	Studies with spatial, co-culture, patient-derived or in vivo evidence were prioritized over descriptive in vitro studies alone.

Continuation Table:

Search domain	Database/ source	Example search string	Screening focus	Evidence prioritization
Lactate and therapy resistance	PubMed; Web of Science Core Collection	("lactate" OR "lactic acid" OR "lactylation") AND ("therapy resistance" OR "chemoresistance" OR "radioresistance" OR "immunotherapy resistance" OR "DNA repair" OR "immune checkpoint blockade") AND ("cancer" OR "tumour" OR "tumor")	Studies linking lactate metabolism, lactate transport, acidosis or lactylation to chemotherapy, radiotherapy, immunotherapy or targeted-therapy resistance.	Studies with causal perturbation, treatment-response models or clinical-response datasets were prioritized.
Lactate and exercise physiology	PubMed; Web of Science Core Collection	("lactate" OR "lactic acid") AND ("exercise" OR "physical activity" OR "training" OR "high-intensity interval training" OR "aerobic exercise" OR "resistance exercise" OR "exerkine" OR "myokine")	Studies addressing exercise-induced lactate production, lactate clearance, lactate threshold, systemic metabolism, inter-organ signalling or training adaptation.	Human exercise studies and mechanistic studies of lactate kinetics were prioritized; purely athletic-performance studies without mechanistic or cancer-supportive-care relevance were excluded.
Exercise oncology and supportive care	PubMed; Web of Science Core Collection	("exercise oncology" OR "physical activity" OR "exercise training") AND ("cancer-related fatigue" OR "cancer-related cognitive impairment" OR "quality of life" OR "survivorship" OR "treatment tolerance" OR "supportive care")	Clinical trials, guidelines and reviews addressing exercise effects on fatigue, physical function, cognition, quality of life, treatment tolerance or survivorship.	Clinical guidelines, randomized trials, meta-analyses and high-quality reviews in cancer populations were prioritized.
Lactate and brain energy metabolism	PubMed; Web of Science Core Collection	("lactate" OR "lactic acid") AND ("brain" OR "neuroenergetics" OR "astrocyte-neuron lactate shuttle" OR "astrocyte neuron lactate shuttle" OR "neuron" OR "astrocyte" OR "microglia" OR "synaptic plasticity" OR "memory")	Studies addressing lactate as a brain substrate, astrocyte–neuron lactate transport, neuronal activity, memory, synaptic plasticity or neuroenergetic regulation.	Mechanistic animal and cellular studies with transporter, metabolic or behavioural testing were prioritized.
Lactate, HCAR1/ GPR81, BDNF and VEGF in neurobiology	PubMed; Web of Science Core Collection	("lactate" OR "lactic acid") AND ("HCAR1" OR "GPR81" OR "BDNF" OR "VEGF" OR "SIRT1" OR "neurovascular" OR "angiogenesis" OR "neuroplasticity") AND ("exercise" OR "brain" OR "memory" OR "cognition")	Studies addressing lactate receptor signalling, BDNF-related plasticity, VEGF-mediated vascular responses, neurovascular regulation or exercise-induced brain adaptation.	Non-cancer mechanistic studies were used as indirect evidence only and were not treated as proof of cancer-specific effects.

Continuation Table:

Search domain	Database/ source	Example search string	Screening focus	Evidence prioritization
Cancer-related fatigue and cognitive impairment	PubMed; Web of Science Core Collection	("cancer-related fatigue" OR "cancer related fatigue" OR "cancer-related cognitive impairment" OR "chemobrain" OR "cancer cognition") AND ("inflammation" OR "mitochondria" OR "neuroinflammation" OR "neuroenergetics" OR "exercise" OR "lactate")	Studies addressing fatigue, cognition, inflammation, mitochondrial dysfunction, neurotoxicity, sleep, distress or treatment-related symptom burden in cancer patients or survivors.	Human cancer studies and clinically relevant animal models were prioritized. Lactate-specific studies were highlighted when available, but absence of direct lactate evidence was explicitly noted.
Psycho-oncology, stress and survivorship	PubMed; Web of Science Core Collection	("psycho-oncology" OR "cancer survivorship" OR "stress resilience" OR "distress" OR "sleep disturbance" OR "pain" OR "allostatic load" OR "adverse childhood experiences") AND ("cancer" OR "survivor" OR "supportive care")	Studies addressing stress biology, distress, pain, sleep disturbance, early-life adversity, trauma-informed care, symptom burden or survivorship outcomes.	Population-based survivorship evidence and studies using validated patient-reported outcomes were prioritized. These studies were used as clinical context, not as direct evidence for lactate signalling.
Histone lactylation	PubMed; Web of Science Core Collection	("histone lactylation" OR "lysine lactylation" OR "H3K18la" OR "H3K9la" OR "H4K16la") AND ("cancer" OR "tumour" OR "tumor" OR "hypoxia" OR "immune" OR "transcription" OR "therapy resistance")	Studies addressing lactate-linked chromatin regulation, transcriptional stress programmes, tumour adaptation, immune regulation or treatment resistance.	Studies with site-specific lactylation evidence, writer/eraser perturbation or functional rescue experiments were prioritized over pan-Kla staining alone.
Non-histone lactylation	PubMed; Web of Science Core Collection	("protein lactylation" OR "non-histone lactylation" OR "lysine lactylation") AND ("DNA repair" OR "MRE11" OR "NBS1" OR "XLF" OR "metabolic enzyme" OR "mitochondria" OR "immune signalling" OR "synaptic protein")	Studies addressing lactylation of DNA-repair proteins, metabolic enzymes, mitochondrial proteins, immune signalling proteins or synaptic proteins.	Studies showing site-specific modification and functional consequences were prioritized.
Exercise-induced lactylation and neural resilience	PubMed; Web of Science Core Collection	("exercise" OR "training" OR "high-intensity interval training") AND ("lactylation" OR "protein lactylation" OR "histone lactylation") AND ("brain" OR "cortex" OR "synapse" OR "microglia" OR "stress resilience" OR "cognition")	Studies addressing exercise-induced lactylation in neural, immune or metabolic tissues and potential links to stress resilience or cognition.	Non-cancer studies were classified as indirect mechanistic evidence and used to generate hypotheses for cancer supportive care.

Continuation Table:

Search domain	Database/ source	Example search string	Screening focus	Evidence prioritization
Google Scholar supplementary searching	Google Scholar	Conceptual combinations of the same search blocks above, including “lactate cancer exercise fatigue cognition lactylation”, “exercise lactate HCAR1 BDNF VEGF brain”, “lactylation DNA repair cancer therapy resistance”, and “cancer survivorship pain adverse childhood experiences”.	Used to identify recent articles, highly cited mechanistic papers, consensus statements and papers not retrieved in database searches.	The first 100–200 results per conceptual search were screened by title and relevance. Peer-reviewed original studies, clinical guidelines and authoritative reviews were prioritized.

Notes: This was a narrative review, not a systematic review or meta-analysis. Therefore, the search strategy was designed to maximize conceptual coverage rather than to generate a pooled quantitative estimate. Evidence was prioritized according to cancer-specificity, mechanistic relevance, consistency across models and availability of causal perturbation evidence. Studies were excluded if they were non-peer-reviewed, unrelated to lactate/lactylation/exercise/neuroenergetics/cancer-supportive-care outcomes, or focused only on athletic performance without mechanistic or clinical relevance to cancer supportive care.