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PD-L1 Lactylation Overturned the Understanding of Lactylations in Hepatocellular Carcinoma

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Abstract:

Hepatocellular carcinoma (HCC) is a leading cause of cancer mortality, and tumor immune evasion mediated by the PD-1/PD-L1 checkpoint axis constitutes a critical therapeutic barrier. Accumulating evidence demonstrates that aberrant tumor metabolism, particularly lactate accumulation and the associated post-translational modification of lysine lactylation (Kla), can modulate PD-L1 expression and function. Recent studies reveal that lysine lactylation modulates PD-L1 through multifaceted mechanisms: histone lactylation at the PD-L1 gene promoter can elevate PD-L1 transcription; lactylation-driven upregulation of factors such as major vault protein (MVP) inhibits PD-L1 proteasomal degradation, increasing its stability; and PD-L1 itself is subject to direct lactylation. Notably, lactylation of PD-L1 at lysine 189 (K189) has been shown to abrogate its nuclear translocation; loss of this modification enables vimentin-mediated nuclear translocation of PD-L1, which in turn promotes tumor progression and metastatic dissemination by triggering de novo cholesterol biosynthesis. These insights underscore a novel link between metabolic reprogramming and immune checkpoint regulation, suggesting that targeting the lactylation pathway in a context-dependent manner across distinct tumor stages may optimize therapeutic outcomes in HCC.

Keywords: PD-L1 lactylation, Hepatocellular carcinoma, Immune evasion, Tumor metabolism

1. Introduction

Hepatocellular carcinoma (HCC) is a highly aggressive malignancy frequently diagnosed at advanced stages, where frequent microvascular invasion and early metastasis are pivotal contributors to its dismal prognosis [1]. A key player in tumor immune evasion is programmed death-ligand 1 (PD-L1), an immune checkpoint ligand commonly overexpressed on cancer cells. By binding to PD-1 on T cells, PD-

L1 dampens anti-tumor immunity, allowing cancer cells to survive and disseminate. High PD-L1 expression in HCC correlates with aggressive clinicopathologic features, including vascular invasion and advanced stage disease [1]. Beyond its canonical immune suppressive function, accumulating evidence supports that PD-L1 harbors tumor cell-intrinsic oncogenic roles that drive malignant progression. In various cancers, PD-L1 signaling within tumor cells can enhance proliferation, epithelial–mesenchymal transition (EMT), invasion, and stemness traits [2]. Against this background of PD-L1–driven immune escape, parallel research has begun to uncover how tumor metabolic reprogramming shapes malignant phenotypes.

One recent breakthrough is the discovery of lysine lactylation, a post-translational modification (PTM) originating from intracellular lactate. In 2019, Zhang et al. elegantly demonstrated that glycolysis-derived lactate can directly transfer lactyl groups to lysine residues within histone tails [3]. Lysine lactylation (Kla) is now recognized as a widespread modification on both histone and non-histone proteins, unveiling a novel regulatory layer underlying the crosstalk between tumor metabolism, cell signaling, and gene expression [4]. Tumor cells typically exhibit the Warburg effect—characterized by enhanced glycolytic flux with concomitant lactic acid accumulation—and HCC is no exception [4]. Given lactate's known role in fostering an immune-tolerant tumor microenvironment and promoting metastasis, lysine lactylation has emerged as a focal point of interest as a molecular conduit linking tumor metabolism to cancer aggressiveness[4]. In contrast to prior studies that focused on lactate's pro-tumorigenic effects or explored lactylation as an independent biological process, this review unites these concepts by focusing on their intersection in HCC. By synthesizing these lines of evidence, we discuss the crosstalk between PD-L1 and lactylation—building upon earlier findings—while highlighting the implications of direct PD-L1 lactylation for therapeutic development.

This review focuses on the emerging intersection of PD-L1 and lysine lactylation in HCC, and how this crosstalk regulates tumor cell invasion and metastasis. We first synthesize current knowledge regarding lactylation in cancer, with a specific emphasis on its pathogenic relevance in HCC. We then discuss recent studies revealing that lactylation can regulate PD-L1 at multiple levels, from epigenetic upregulation of PD-L1 gene expression to direct modification of the PD-L1 protein, thereby influencing HCC cells' invasive and metastatic behavior. Finally, we elaborate on the therapeutic potential of targeting this newly identified PD-L1-lactylation axis for HCC clinical management. By integrating these emerging insights, this review underscores the significance of direct PD-L1 lactylation as a novel paradigm for understanding HCC progression. Elucidating this axis could reveal new biomarkers of tumor aggressiveness and identify therapeutic vulnerabilities, highlighting the potential impact of this work on future HCC management.

2. Lysine Lactylation

Lysine lactylation denotes the covalent conjugation of a lactyl moiety (derived from cellular lactate) to the ε-amino group of lysine residues within target proteins. Tumor cells exhibiting elevated glycolytic flux generate substantial lactate pools, which serve as a substrate to augment global lactylation levels. Global lactylome analyses have corroborated that lactylation is pervasive in HCC tumors and facilitates malignant progression [4]. In a 2023 study by Yang et al., proteomic profiling of HCC tissues identified hundreds of lactylated proteins involved in metabolic adaptation, indicating that the lactylation "code" is extensively written in liver tumors to support their growth and survival [5]. Notably, specific lactylation events have been functionally associated with key cancer phenotypes. For example, SIRT3 activation induces apoptosis and tumor suppression in part by delactylating Cyclin E2 [6]. Lactylation of Cyclin E2 at lysine-348 (K348) enhances HCC cell proliferation, whereas the mitochondrial deacetylase SIRT3 mediates the removal of this lactyl mark[6]. This suggests lactylation of certain proteins abrogates their tumor-suppressive functions, thereby promoting tumor proliferation. Moreover, some proteins' lactylations can also modulate tumor invasion and metastatic potential. For instance, adenylate kinase 2 lactylation at K28 was reported to suppress mitochondrial function and drive metastatic behavior in HCC models [7]. Recent studies have uncovered a multitude of lactylation substrates implicated in invasive processes, encompassing cytoskeletal proteins and enzymes involved in extracellular matrix (ECM) remodeling pathways[7].

Beyond direct lactylation-mediated abrogation of tumor-suppressive pathways. Another mechanism in which lactylation can promote tumor proliferation involves the epigenetic upregulation of pro-metastatic genes. Histone lactylation functions as an epigenetic mark that potentiates gene transcription[3]. For instance, p300/CBP was identi-

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fied as a major histone lactyltransferase using lactyl-CoA as a donor [8][9]. Conversely, class I histone deacetylases (HDAC1-3) and sirtuins act as "erasers" or delactylases to remove lactyl groups [9]. Through these enzymes, cells can dynamically regulate lactylation in response to metabolic cues. Huang et al. (2025) reported that under sublethal stress conditions (incomplete microwave ablation of HCC), rising lactate levels led to increased H3K18 lactylation (H3K18la) in tumor cells, which in turn enhanced transcription of NFS1, a gene encoding a cysteine desulfurase that protects cells from ferroptotic cell death [8]. Consequently, HCC cells acquired enhanced ferroptosis resistance and increased metastatic capacity; NFS1 knockdown abrogated the metastasis-promoting effect of lactylation and sensitized cells to therapeutic interventions [8]. This study provides direct evidence that lactylation can drive metastasis in HCC by activating genes that help tumor cells survive under stress and colonize new sites. Taken together, these findings establish lactylation as a pivotal regulator of malignant progression: by reprogramming gene expression and protein function in response to metabolic cues, lactylation can orchestrate cancer cell proliferation, invasiveness, and metastatic potential [9].

3. Lactate and PD-L1 Interplay

Tumor metabolic reprogramming and immune evasion are inextricably intertwined. In HCC patients, elevated lactylation has been correlated with poor overall survival and resistance to immune checkpoint inhibitors (ICIs) [10]. Lactate accumulation in the tumor microenvironment not only intrinsically fosters metastatic dissemination but also establishes an immunosuppressive niche that enables disseminated tumor cells to survive. High lactate levels impair cytotoxic T lymphocytes and NK cells, skew macrophages to immunosuppressive (M2) phenotypes, and generally blunt anti-tumor immunity [4]. Ding et al. delineated a metabolic-epigenetic circuitry centered on PD-L1 in HCC. They first focused on protein arginine methyltransferase 3 (PRMT3), an enzyme that they found to be upregulated in HCC and linked to worse outcomes [4]. PRMT3 promotes aerobic glycolysis in HCC cells via methylation-dependent activation of metabolic enzymes, leading to excessive lactate production [4]. The increased lactate then acted as a substrate for lactylation. PRMT3 overexpression elevated global lactylation levels, particularly H3K18 lactylation at the PD-L1 gene promoter, as shown by chromatin immunoprecipitation assays [4]. H3K18 potentiates PD-L1 transcriptional activity, leading to enhanced PD-L1 expression on tumor cells that further reinforces tumor immune evasion [4]. Moreover, anti-PD-L1 therapy abrogated the tumor-promoting effects of PRMT3 in vivo, underscoring PD-L1 as a critical downstream effector of this metabolic-epigenetic pathway [4]. This study establishes a clear causal chain: PRMT3 → elevated lactate → histone lactylation (H3K18la) → PD-L1 gene upregulation → immune evasion and tumor progression. It also generalizes the paradigm that histone lactylation functions as a molecular conduit linking oncogenic metabolism to immune checkpoint regulation.

Complementary evidence comes from a recent study by Liu et al., who demonstrated that histone lactylation induces immune checkpoint expression, thereby reinforcing tumor immune escape. Specifically, using multi-omics analyses, the authors identified major vault protein (MVP) that was shown to bind the E3 ubiquitin ligase β-TrCP, preventing it from degrading PD-L1 protein [10]. When lactate levels are high, histone lactylation upregulates MVP, which then stabilizes PD-L1 by blocking its proteasomal turnover [10]. This cascade results in tumor cells maintaining high surface PD-L1, effectively impairing infiltrating T-cell function and conferring resistance to PD-1/PD-L1 blockade therapy [10]. Notably, inhibition of lactylation in HCC models enhanced CD8+ T-cell infiltration and cytokine secretion, while restoring sensitivity to anti-PD-1 therapy [10]. These findings reveal that lactylation drives an immune-evasive program in HCC by ensuring PD-L1 remains abundant on tumor cells [4][10].

4. PD-L1 Lactylation

While lactylation can regulate PD-L1 availability by controlling its gene expression or stability, a recent seminal study demonstrates that PD-L1 itself is a direct substrate for lysine lactylation, with profound implications for HCC invasive and metastatic potential. Wang et al. [11] reported for the first time that PD-L1 protein is subject to lysine lactylation, and that this modification alters PD-L1's localization and pro-tumor activities [11]. In HCC cell lines and tumor samples, PD-L1 was found to be lactylated at lysine 189 (K189), catalyzed by the acetyltransferase p300 [11]. Lactylation at K189 impedes PD-L1 nuclear translocation, effectively sequestering PD-L1 within the plasma membrane and cytosolic compartments [11]. This has important implications: normally, we think of PD-L1 as a membrane ligand, but emerging evidence suggests

PD-L1 can also function in the nucleus to modulate gene transcription and other signaling pathways [2]. Indeed, nuclear PD-L1 has been linked to pro-tumor processes such as enhancing angiogenesis via EGR1 or promoting cell proliferation [12]. In HCC, Wang et al. observed that when PD-L1 was de-lactylated (or K189 was not lactylated), it interacted with vimentin and was shuttled into the nucleus [11]. Nuclear PD-L1 then acts as a transcriptional co-activator for genes involved in de novo cholesterol biosynthesis [11]. It upregulated SQLE, the gene encoding squalene epoxidase, a rate-limiting enzyme in cholesterol production. This led to increased cholesterol synthesis in cancer cells, which in turn drove tumor growth and likely provided a source of structural components for rapidly proliferating and migrating cells [11]. Cholesterol-enriched membranes and activated metabolic pathways support the bioenergetic and structural demands of cell migration, while vimentin—a classic marker and mediator of EMT—chaperones PD-L1 to the nucleus upon PD-L1 de-lactylation [11]. Functionally, PD-L1 de-lactylation was associated with accelerated tumor growth and higher tumor grade. In Wang et al.'s clinical HCC specimens, lower PD-L1 K189 lactylation was shown in higher-grade tumors (negative correlation, $\chi^2 = 23.55$, $P < 0.01$, $n = 95$), implying that more aggressive HCCs tend to have more PD-L1s in a de-lactylated state [11]. HCC patients with low or absent PD-L1 K189. In HCC, Wang et al. observed that when PD-L1 was de-lactylated (or K189 was not lactylated), it interacted with vimentin and was shuttled into the nucleus [11]. Nuclear PD-L1 then acts as a transcriptional co-activator for genes involved in de novo cholesterol biosynthesis [11]. It upregulated SQLE, the gene encoding squalene epoxidase, a rate-limiting enzyme in cholesterol production. This led to increased cholesterol synthesis in cancer cells, which in turn drove tumor growth and likely provided a source of structural components for rapidly proliferating and migrating cells [11]. The Cancer Genome Atlas (TCGA) dataset [11]. By keeping PD-L1 primarily at the cell surface, K189 lactylation might restrain some of PD-L1's pro-tumor intracellular signaling, confining it to its immune checkpoint role. Conversely, loss of that modification triggers PD-L1's full oncogenic potential in supporting invasion and metabolic adaptation. This finding broadens the understanding of the crosstalk between lactylation and PD-L1: lactylation not only modulates PD-L1 expression levels but also dictates its subcellular localization and functional repertoire. It underscores that post-translational modifications of PD-L1 can dictate whether it merely serves as an immune shield or additionally acts as a pro-metastatic factor inside the cancer cell.

5. Discussion

Elevated lactate-driven lysine lactylation is a pro-tumor mechanism in HCC, leading to an early consensus that global lactylation inhibition might exert uniform therapeutic efficacy [6][10]. The recent discovery of PD-L1 K189 lactylation in HCC challenged this paradigm. HDAC2-mediated delactylation of PD-L1 K189 triggers PD-L1's translocation into the nucleus [11]. Nuclear PD-L1 then functions as a transcriptional co-regulator, notably upregulating *SQLE*, which accelerates liver tumor growth [11]. Importantly, analysis of clinical HCC specimens reveals that loss of PD-L1 lactylation correlates with high-grade HCC which has predominantly delactylated PD-L1 [11]. In contrast to the pro-tumor influence of histone lactylation, here lactylation plays a tumor-suppressive role by retaining PD-L1 within the membrane-cytosolic compartment, thereby abrogating the activation of a pro-proliferative cholesterol biosynthesis program [11]. A global inhibition of lactylation might remove this "brake" on tumor growth by facilitating PD-L1 delactylation and nuclear accumulation. This new theory necessitates a more nuanced therapeutic strategy.

Future HCC treatments will likely turn from global lactate blockade to context-specific modulation of lactylation pathways. One approach involves the selective targeting of histone lactylation. There is precedent for such compartmental selectivity. SIRT3 activation (e.g., by honokiol) can erase deleterious lactylation on nuclear or cytosolic targets like cyclin E2 [6]. By contrast, broad metabolic interventions such as LDH inhibitors or fasting mimetics influence a wide range of metabolism, raising the risk of off-target effects such as triggering PD-L1 delactylation. Thus, precision targeting of lactylation "writers" or "erasers" is paramount. Drug development may focus on enzymes unique to its contexts. For example, inhibiting a nuclear-localized lactyl-CoA synthetase to attenuate histone lactylation, or targeting HDAC2's delactylase activity in the cytosol to preserve PD-L1 K189 lactylation.

Spatially or functionally restricting PD-L1 activity also holds therapeutic promise. Given that nuclear PD-L1 promotes tumor growth via cholesterol biosynthesis, a possible strategy is to prevent PD-L1's nuclear entry or action without impairing its lactylation status[11]. This could be

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achieved by targeting the chaperone complexes mediating PD-L1 nuclear translocation. For example, disrupting the interaction between PD-L1 and vimentin or other transport mediators could sequester PD-L1 at the cell membrane or within the cytoplasm. Another angle is to directly disrupt the downstream consequences of PD-L1 delactylation. Previous studies by Wen et al. demonstrated that inhibiting SQLE can restore anti-PD-1 immunotherapy efficacy in HCC [13]. This finding can now be interpreted as counteracting the oncogenic effects of PD-L1 delactylation. Since the nuclear PD-L1–YY1 complex specifically boosts SQLE transcription, targeting cholesterol synthesis might counteract the outcome of PD-L1 delactylation, therefore restoring anti-PD-1 immunotherapy efficacy in HCC. This suggests that combination therapy—such as combining a cholesterol-lowering agent with anti-PD-L1 therapy—may yield clinical benefits for HCC patients.

6. Conclusion

In synthesis of accumulating evidence, PD-L1 K189 lactylation orchestrates the subcellular partitioning of PD-L1 between the plasma membrane and nuclear compartment. When lactylation levels change, PD-L1 may shift localization. Abundant lactate not only upregulates PD-L1 expression, but also maintains PD-L1 K189 lactylation, thereby constraining aberrant pro-tumor signaling. As tumors progress, if a delactylase like HDAC2 is overactive or lactyl-CoA donors are depleted, PD-L1 could lose its lactyl modification at K189 and translocate to the nucleus, acting as a transcriptional co-factor to promote survival pathways (cholesterol synthesis, angiogenesis). This would confer metastatic cells with supplementary oncogenic advantages: better membrane biosynthesis, protection from ferroptosis (via cholesterol upregulation), and enhanced angiogenesis to support secondary tumor outgrowth. In essence, PD-L1 de-lactylation might be a switch that shifts a cell from a primarily immune-evasive mode to a fully aggressive, metastatic mode. However, this emerging field still faces several limitations before it translates into clinical improvements over conventional therapies. Most current evidence comes from preclinical models or small patient cohorts, so the clinical relevance of these findings has yet to be fully established. Future studies should address these gaps by validating PD-L1 lactylation patterns in large-scale HCC patient cohorts and refining experimental models to selectively target this modification without off-target effects.

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