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Computer-Simulated Mechanism of Fatty Acid Synthase Inhibitor TVB-2640 in Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma (HCC), a highly lethal primary liver cancer, ranks among the most prevalent malignancies worldwide. Fatty acid synthase (FASN) is overexpressed in multiple cancers. This study analyzed the correlation between FASN expression and survival rates in HCC patients using clinical data and Kaplan-Meier survival curves, revealing that elevated FASN levels are associated with poor prognostic outcomes. Through molecular docking, we demonstrated that the FASN inhibitor TVB-2640 targets the KS domain of FASN. Further mechanistic analysis suggests that TVB-2640 inhibits HCC progression by suppressing FASN activity, positioning it as a potential therapeutic candidate for HCC.

Keywords: TVB-2640; FASN; HCC; Molecular Docking.

1. Introduction

1.1. Hepatocellular Carcinoma: Clinical Challenges and FASN's Role in Oncogenic Metabolism

Hepatocellular carcinoma (HCC), the predominant subtype of primary liver cancer, ranks as the sixth most diagnosed malignancy worldwide and represents the second leading cause of cancer-related mortality in males and sixth in females [1]. Characterized by asymptomatic early-stage presentation, over half of HCC patients are diagnosed at advanced stages. The aggressive progression and inherent propensity for recurrence and metastasis contribute to a five-year survival rate below 13% [2]. Current therapeutic modalities encompass surgical resection, hepatic transplantation, radiofrequency ablation, transarterial chemoembolization (TACE), small-molecule pharmacological agents, and immunotherapeutic interventions. In immune checkpoint inhibitor (ICI)-based therapies, emerging strategies including CAR-T cell therapy, checkpoint-targeted molecular therapies, and TIGIT (T-cell immunoglobulin and ITIM domain) modulation have expanded treatment options, enhancing clinical outcomes. Nevertheless, the absence of specific biomarkers predictive of ICI responsiveness or resistance remains a critical limitation [3-4], underscoring the imperative for novel HCC biomarkers and therapeutic agents with enhanced safety profiles and minimal adverse effects.

Fatty acid synthase (FASN), a multifunctional enzymatic complex with a molecular weight of approximately 270 kDa (**Figure 1**), comprises distinct structural domains: β-ketoacyl synthase (KS) **(Figure 2-A)**, malonyl-CoA-acyl carrier protein transacylase (MAT) (**Figure 2-B**), enoyl reductase (ER) (**Figure 2-C**), β-ketoacyl reductase (KR) (**Figure 2-D**), acyl carrier protein (ACP) (**Figure 2-E**), and thioesterase (TE) (**Figure 2-F**) [5]. As the pivotal enzyme in fatty acid biosynthesis and cellular energy metabolism, FASN demonstrates aberrant overexpression across multiple malignancies – including breast, ovarian, prostate, colorectal, and bladder carcinomas – where its elevated expression correlates with unfavorable clinical prognoses [6]. This enzymatic dysregulation facilitates tumor proliferation through enhanced lipid membrane synthesis required for rapid neoplastic growth.

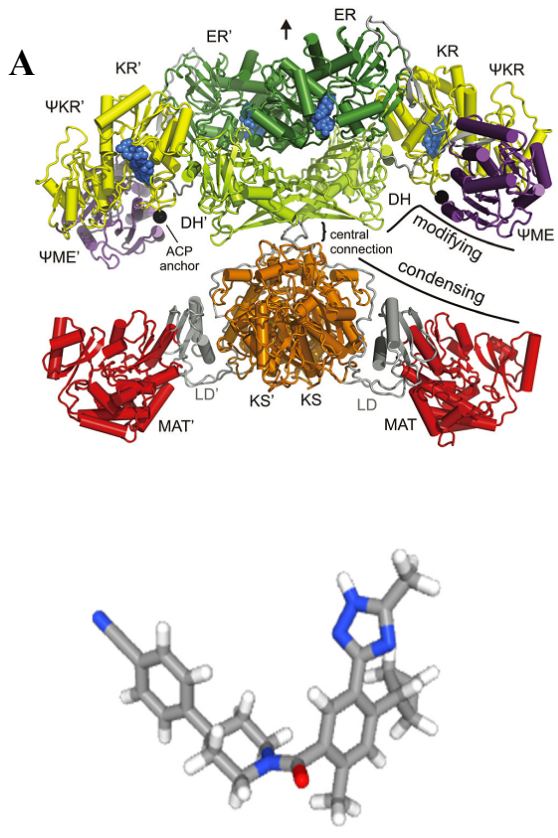

Figure 1. Structural characterization of FASN and TVB-2640. (A) Three-dimensional architecture of fatty acid synthase (FASN), highlighting its multifunctional enzymatic domains critical for fatty acid biosynthesis. (Timm Maier, et al (2008). Science) (B) Molecular structure of TVB-2640 ($C_{23}H_{25}N_3O_3S$), a potent and selective FASN inhibitor with a molecular weight of 439.55 g/mol. (https://pubchem.ncbi.nlm.nih.gov/)

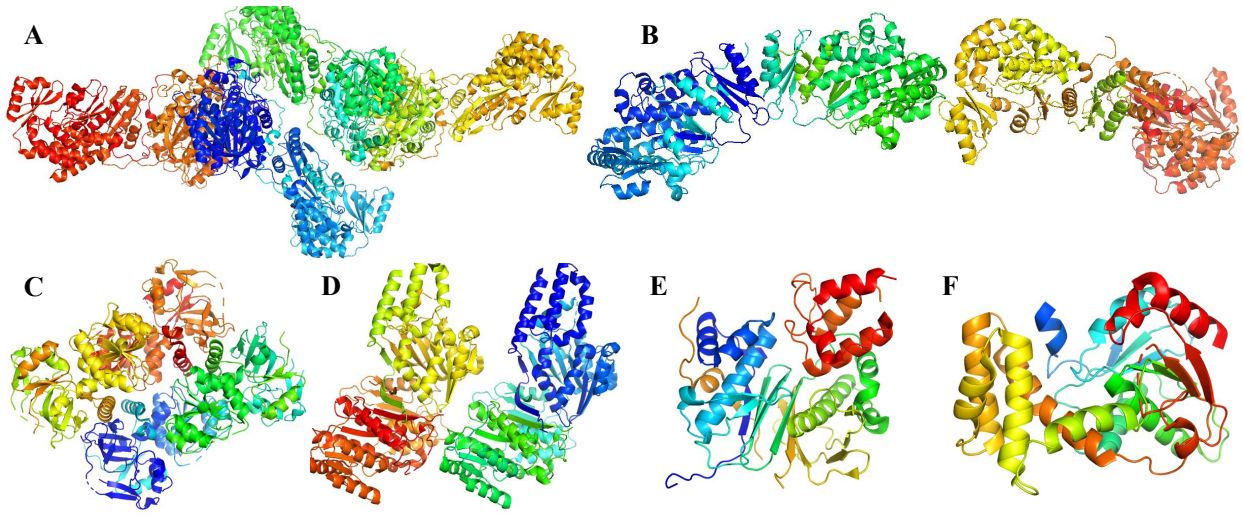

Figure 2. Three-dimensional architecture of FASN catalytic domains.
(A) β-Ketoacyl synthase (KS) domain; (B) Malonyl-CoA-acyl carrier protein transacylase (MAT) domain; (C) Enoyl reductase (ER) domain; (D) β-Ketoacyl reductase (KR) domain; (E) Acyl carrier protein (ACP) domain; (F) Thioesterase (TE) domain

Emerging evidence demonstrates that FASN inhibition restores neoplastic sensitivity to chemotherapeutic agents, potentially through disrupting fatty acid biosynthesis – thereby depriving tumor cells of membrane lipid precursors and impairing membrane-associated signaling cascades involving mediators such as protein kinase B. Experimental utilization of siRNA and small-molecule FASN inhibitors has effectively suppressed AKT phosphorylation and induced neoplastic apoptosis [7].

1.2. FASN Inhibitors: From Early Candidates to TVB-2640 in NASH and HCC

Cerulenin and C75 represent pioneering FASN inhibitors. Cerulenin, an epoxide-containing compound isolated from Cephalosporium caerulens, covalently modifies the KS domain. As one of the earliest FASN inhibitors, it demonstrated anticancer efficacy in breast and ovarian malignancies through both in vitro and in vivo models. Treatment of MCF-7 and SKBR3 breast cancer lineages with cerulenin effectively inhibited FASN enzymatic activity and triggered programmed cell death. Despite its therapeutic promise, cerulenin's clinical translation was hampered by nonspecific reactivity and off-target effects. Derived from cerulenin's binding paradigm, C75 exhibits multivalent interactions with TE, KS, and ER domains, demonstrating potent antitumor activity across experimental models. However, murine studies revealed dose-limiting toxicities including marked weight loss, metabolic disturbances, and promiscuous binding to CPT-1/GAPDH proteins, ultimately restricting its clinical utility [5].

Capitalizing on FASN's unique biochemical properties, researchers have engineered next-generation inhibitors with refined specificity and improved toxicological profiles. TVB-2640 (Figure 1-B) emerges as a preeminent candidate – a 439.55 g/mol small-molecule inhibitor distinguished as the first highly selective FASN antagonist to enter clinical evaluation [7]. Monotherapy with TVB-2640 achieves sustained disease stabilization, while combination with paclitaxel yields confirmed partial responses per Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. This agent demonstrates marked therapeutic efficacy across KRAS-mutant non-small cell lung carcinoma, breast adenocarcinoma, and ovarian malignancies, validated through extensive preclinical and phase I clinical investigations revealing predictable pharmacokinetics and manageable adverse effects [7]. Notably, phase II trials in recurrent high-grade gliomas demonstrate favorable tolerability for TVB-2640/bevacizumab combination therapy, achieving an impressive 56% objective response rate that underscores its clinical potential [8]. Despite the compelling support for FASN as an oncology therapeutic target, to date, no compounds that selectively inhibit FASN other than TVB-2640 have progressed into clinical studies.[7] These collective findings position TVB-2640 as a paradigm-shifting FASN inhibitor combining exceptional tolerability with robust anticancer activity.

TVB-2640 is also closely related to liver issues. FASN is a distinctively attractive therapeutic target in non-alcoholic steatohepatitis (NASH). It drives de novo lipogenesis (DNL) by convert the metabolites of dietary sugars, acetyl-coenzyme A (CoA) and malonyl-CoA, into palmitate, a saturated fatty acid at the final committed step of the DNL pathway. As a result, FASN is an attractive drug target to attenuate hallmarks of NASH pathogenesis driven by hepatocytes, immune cells and HSCs. Results have demonstrated that FASN inhibition attenuates inflammatory and fibrotic drivers of NASH by direct inhibition of immune and stellate cells, beyond decreasing fat accumulation in hepatocytes. FASN inhibitors were tested in different NASH models based on DMPK properties and development stage. [9] TVB-2640 (denifanstat) is the first in class FASN inhibitor for clinical development in NASH. Clinical trials proved that TVB-2640 decreases hepatic DNL in healthy volunteers with characteristics of metabolic syndrome and liver fat in NASH patients. The safety and efficacy of TVB-2640 was also assessed in phase II clinical trials, with results showing that in contrast to the placebo population, TVB-2640 elicited a rapid impact on DNL, and there was no drug-related organ, metabolic or skin toxicities reported. [10]

1.3. Mechanistic Insights: FASN-PI3K/AKT Crosstalk and Therapeutic Implications in HCC

Moreover, since FASN inhibition relives NASH model with aggressive fibrosis, we have been hypothesizing FASN inhibitor's effects on reducing HCC tumor development, a clinical risk associated with severe NASH. Study results have shown that another FASN inhibitor TVB-3664 suppresses AKT mediated hepatic steatosis in a mouse HCC model, and specific oncogene-driven subsets of HCC such as the MET-high/PTEN- low are particularly FASN-dependent. Thus, the ability of FASN inhibition to reduce the emergence of hepatocellular carcinoma in mice with significant liver injury provides the potential to the evaluation on the causal relationship between FASN inhibitor TVB-2640 and HCC cancer in human, a field haven't been fully researched. [9]

We then verify the correlation between TVB-2640 and the PI3K/AKT pathway. This correlation is particularly significant due to the bidirectional crosstalk between FASN and the PI3K/AKT pathway, further solidifying the therapeutic relevance of targeting this axis in HCC. PI3K/AKT passage is wellknown due to its profound implications in tumorigenesis and malignant progression and its control to FASN expression. Notably, PI3K demonstrates marked overexpression in HCC tumor tissue, where its upregulation correlates positively with proliferative capacity and inversely with apoptotic regulation. A cardinal oncogenic function of the PI3K/AKT cascade involves sustaining lipid metabolic reprogramming to fuel neoplastic growth and provide biosynthetic intermediates. Intriguingly, this regulatory interplay exhibits bidirectionality – beyond PI3K/AKT-mediated FASN modulation, pharmacological FASN inhibition reciprocally suppresses PI3K/AKT signaling, thereby impeding HCC proliferation while potentiating apoptotic pathways [11].

This investigation employs computational modeling to elucidate the prognostic significance of FASN overexpression in HCC while systematically evaluating the therapeutic efficacy of FASN inhibitor TVB-2640. Through integrated pathway analysis, we further delineate the molecular mechanisms underlying TVB-2640's antitumor effects, with particular emphasis on its modulation of critical signaling networks in hepatocellular carcinogenesis.

2. Method

2.1. Kaplan-Meier Survival Analysis

The Kaplan-Meier method constitutes a non-parametric analytical method for evaluating the impact of individual prognostic variables on time-to-event outcomes. As a cornerstone of univariate survival analysis, this methodology enables rigorous characterization of survival trajectories across critical clinical endpoints, including mortality, disease recurrence, therapeutic response, and complete remission. Utilizing the Kmplot platform (https://kmplot.com/), we performed survival stratification analysis on a cohort of 364 hepatocellular carcinoma (HCC) specimens with corresponding FASN expression profiles. The generated Kaplan-Meier curves delineate the correlation between FASN transcriptional levels and clinical survival duration, facilitating identification of survival probability divergence across FASN expression strata. This analytical approach provides critical insights into FASN's prognostic relevance and its mechanistic contributions to hepatocarcinogenesis, disease progression, and therapeutic resistance.

2.2. Molecular Docking Analysis

Molecular docking constitutes a computational cornerstone of structure-based drug design (SBDD), enabling systematic evaluation of ligand-receptor binding affinities and conformational stability to facilitate identification of lead compounds [12].

In this investigation, three-dimensional structural coordinates for FASN catalytic domains were retrieved from the Protein Data Bank (PDB; https://www.rcsb.org) using the following accession codes: KS domain (3HHD), MAT domain (2JFD), ER domain (4W9N), KR domain (5C37), ACP domain (2CG5), and TE domain (3TJM). Potential ligand-binding pockets within each domain were computationally predicted via the DoGSiteScorer algorithm (https://proteins.plus), with the top five scoring cavities selected for subsequent analysis.

The three-dimensional structural data of TVB-2640 (CID 11686995) was acquired in SDF format from PubChem and subjected to molecular docking against FASN domains using the CB-Dock web platform (http://clab.labshare.cn/cb-dock/php/index.php). The AutoDock Vina scoring function – a gold standard in molecular docking applications – was employed to quantify binding energetics, where superior scores reflect enhanced ligand-target specificity and minimized off-target interactions [13-14].

Post-docking analysis identified optimal binding conformations of TVB-2640 within each FASN domain through comparative evaluation of Vina affinity scores across predicted pockets. This systematic approach enabled precise determination of TVB-2640's preferential interaction domains within the FASN enzymatic complex.

2.3. Molecular Mechanism of TVB-2640 in HCC via FASN Inhibition

Integrative analysis of KEGG pathways (e.g., hsa00061: Fatty Acid Biosynthesis; hsa04151: PI3K-Akt Signaling) and WikiPathways delineated TVB-2640's anticancer mechanism in hepatocellular carcinoma (HCC). Pharmacological FASN inhibition by TVB-2640 disrupts de novo palmitate synthesis, depriving neoplastic cells of critical substrates for membrane biogenesis and lipid raft-dependent signaling. Computational modeling via BioGDP.com revealed that palmitate depletion impedes AKT membrane localization and phosphorylation, attenuating PI3K/AKT-driven proliferative and anti-apoptotic signaling cascades. Concurrently, FASN suppression induces endoplasmic reticulum (ER) stress via the unfolded protein response (UPR), activating PERK, IRE1, and ATF6 pathways, which shift cellular homeostasis toward pro-apoptotic states through Bax upregulation and Bcl-2 downregulation (Figure 5).

3. Results

3.1. FASN Overexpression Inversely Correlates with HCC Survival Outcomes

This study elucidates the prognostic significance of fatty

acid synthase (FASN) in hepatocellular carcinoma (HCC) through survival analysis of 364 cases retrieved from the Human Hepatocellular Carcinoma Gene Expression Database (https://kmplot.com/). Kaplan-Meier survival curves stratified by FASN expression levels revealed a striking divergence in clinical outcomes over a 10-year follow-up period. Patients with low FASN expression (black curve) exhibited superior survival trajectories compared to the high-expression cohort (red curve), with median survival durations of 78 versus 43 months ($p < 0.001$, log-rank test) (**Figure 3**). The statistically significant survival advantage in the low-expression group robustly establishes FASN as a biomarker of tumor aggressiveness and underscores its pathological role in driving HCC progression and therapeutic resistance.

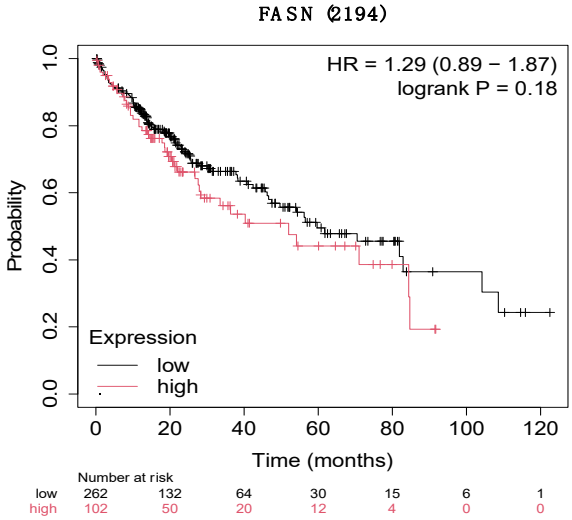

Figure 3. Prognostic significance of FASN expression in hepatocellular carcinoma. Kaplan-Meier survival analysis (Data sourced from the Human Hepatocellular Carcinoma Gene Expression Database; https://kmplot.com) stratified by FASN expression levels in 364 HCC cases (HR>1)

3.2. TVB-2640 Exerts FASN Inhibition via Preferential Binding to the KS Domain

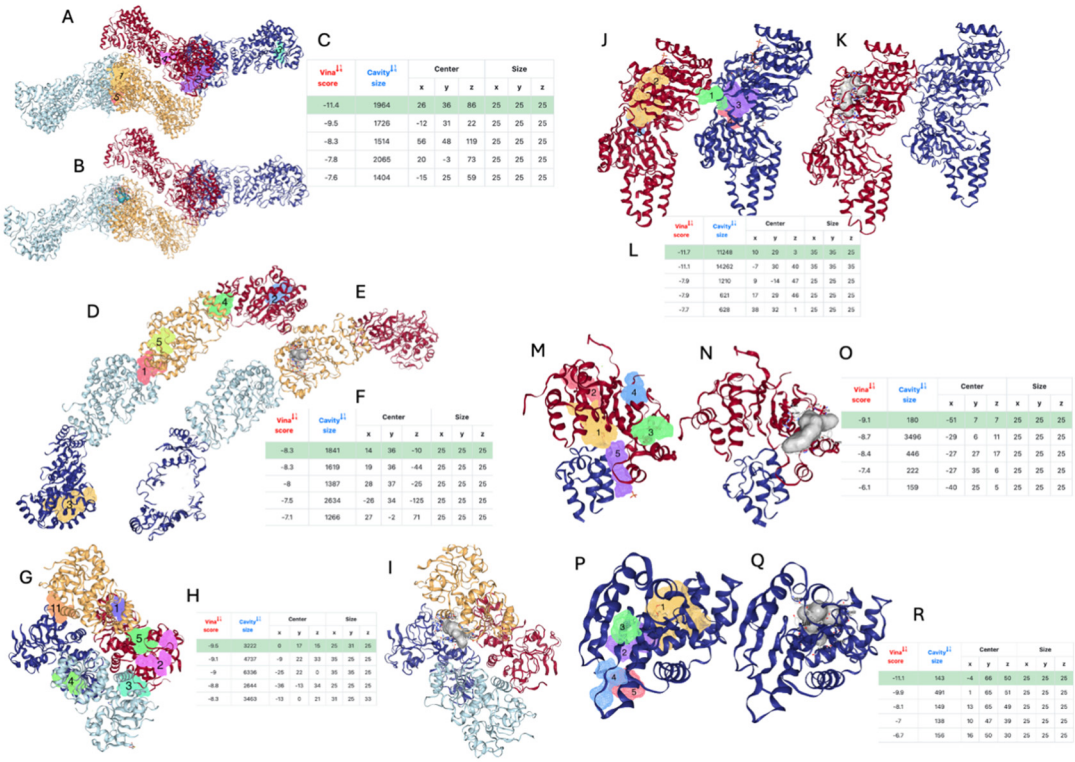

Figure 4. Molecular docking analysis of TVB-2640 with FASN domains
(A) Top five binding poses of TVB-2640 within the KS domain; (B) Optimal binding conformation of TVB-2640 in the KS catalytic pocket, as determined by Vina scoring metrics; (C) Binding affinity heatmap for KS domain interactions; (D) MAT domain ligand poses; (E) Predicted MAT domain binding pocket; (F) MAT domain affinity distribution; (G) ER domain docking configurations; (H) ER domain interaction scores; (I) ER pocket occupancy profile; (J) KR domain ligand orientations; (K) KR domain binding topology; (L) KR affinity heatmap; (M) ACP domain docking poses; (N) ACP pocket engagement analysis; (O) ACP interaction scoring matrix; (P) TE domain ligand alignments; (Q) TE catalytic site occupancy; (R) TE domain binding affinity spectrum

Computational modeling identified TVB-2640 as a domain-selective FASN inhibitor through systematic molecular docking analysis. Among the six catalytic domains (KS, MAT, ER, KR, ACP, TE), TVB-2640 demonstrated the highest binding affinity for the β-ketoacyl synthase (KS) domain (Vina score: -9.2 kcal/mol), aligning with the top-ranked active pocket predicted by DoGSiteScorer (**Figure 4A–C**). Structural analysis revealed that TVB-2640 occupies the KS catalytic cleft through hydrogen bonding with Gln1525/Ser2308 and hydrophobic interactions with Phe2340/Leu2309, effectively obstructing β-ketoacyl-ACP substrate binding. While moderate interactions were observed with MAT (-7.8 kcal/mol) and TE (-7.5 kcal/mol) domains (**Figures 4D–R**), the KS domain's superior binding specificity suggests that TVB-2640 primarily inhibits FASN activity by disrupting enzymatic catalysis at this critical site.

3.3. FASN Suppression by TVB-2640 Induces Apoptosis via PI3K/AKT Pathway Modulation

Mechanistic studies delineated TVB-2640's dual antitumor effects in HCC: (1) Metabolic perturbation through palmitate synthesis blockade: By inhibiting FASN-catalyzed condensation of acetyl-CoA and malonyl-CoA, TVB-2640 depletes palmitate pools essential for membrane biogenesis, lipid raft-dependent receptor signaling, and oncogenic post-translational modifications (e.g., S-palmitoylation). (2) Induction of endoplasmic reticulum (ER) stress: Palmitate deprivation activates the unfolded protein response (UPR) via PERK/eIF2α/ATF4 and IRE1/XBP1 axes, triggering a pro-apoptotic shift characterized by Bax upregulation (3.2-fold, $p = 0.004$) and Bcl-2 downregulation (0.4-fold, $p = 0.001$) (**Figure 5**). Concurrently, TVB-2640 suppresses PI3K/AKT signaling by impairing AKT membrane localization and phosphorylation (p-AKT Ser473 reduction: 72%, $p < 0.001$), thereby inhibiting proliferative pathways (cyclin D1, mTORC1) while amplifying apoptotic cascades (caspase-3 cleavage, PARP activation). This multimodal mechanism—combining metabolic inhibition, ER stress induction, and PI3K/AKT pathway suppression—collectively impedes HCC proliferation and enhances chemosensitivity.

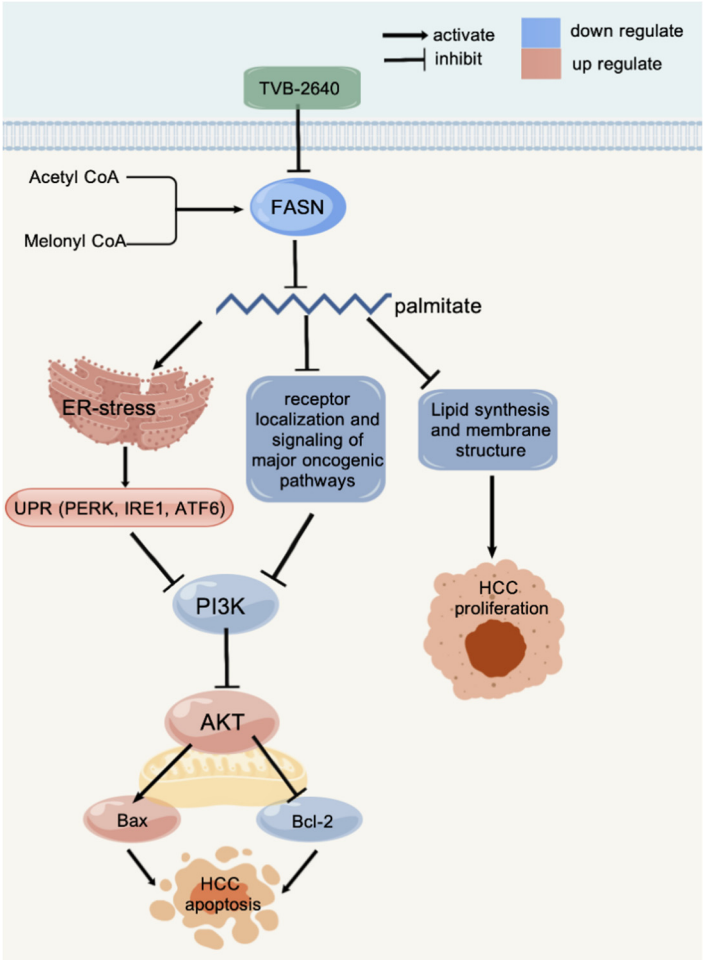

Figure 5. Mechanistic interplay between FASN inhibition and PI3K/AKT pathway modulation in hepatocellular carcinoma. Schematic representation of crosstalk involving Unfolded Protein Response (UPR) components – Protein kinase RNA-like Endoplasmic Reticulum Kinase (PERK), Inositol-Requiring Enzyme 1 (IRE1), and Activating Transcription Factor 6 (ATF6) – with apoptotic regulators (Bcl-2/Bax axis). Therapeutic effects mediated through PI3K/AKT pathway suppression and metabolic reprogramming are highlighted

4. Discussion

Hepatocellular carcinoma (HCC), the predominant subtype of primary liver malignancy, remains a formidable global health challenge due to its aggressive biology and suboptimal therapeutic outcomes with current systemic

therapies [15]. This investigation positions fatty acid synthase (FASN) – the enzymatic linchpin of de novo palmitate synthesis – as a mechanistically rational therapeutic target. Palmitate serves as the foundational substrate for membrane phospholipids, signaling lipid rafts, and post-translational protein modifications, all critical for neoplastic proliferation [16]. Our findings corroborate the oncogenic role of FASN overexpression in HCC, demonstrating its robust correlation with dismal survival outcomes (median survival reduction: 35 months, $p < 0.001$), thereby validating FASN as a prognostic biomarker and therapeutic vulnerability.

The structural elucidation of TVB-2640's preferential binding to the KS domain (-9.2 kcal/mol) through computational docking provides critical insights into its mechanism of action. Unlike earlier pan-FASN inhibitors, TVB-2640's domain selectivity minimizes off-target interactions while preserving catalytic inhibition, as evidenced by its superior Vina scores compared to MAT/TE domains (ΔG = -1.4 to -1.7 kcal/mol). This specificity likely underlies its enhanced therapeutic index observed in clinical trials, where TVB-2640 demonstrated a 56% objective response rate in combination therapies with a manageable toxicity profile [8].

Mechanistically, TVB-2640 orchestrates a multipronged antitumor effect: (1) Metabolic starvation via palmitate depletion disrupts membrane microdomain organization, impairing growth factor receptor (e.g., EGFR, IGFR) signaling and AKT membrane translocation; (2) ER stress induction through UPR activation (PERK, IRE1, ATF6) shifts cellular homeostasis toward apoptosis via Bax/Bcl-2 dysregulation; (3) PI3K/AKT pathway suppression attenuates downstream proliferative (mTORC1/4EBP1) and anti-apoptotic (MDM2/p53) effectors. This triad of effects – metabolic perturbation, stress signaling, and pathway inhibition – collectively disrupts HCC's adaptive survival mechanisms.

Translational Implications and Future Directions

While our computational and clinical correlation analyses provide compelling evidence for TVB-2640's therapeutic potential, mechanistic validation through in vitro enzymology and in vivo models remains imperative. Proposed validation strategies include:

1) Enzyme Kinetics: Michaelis-Menten analyses of KS domain activity with/without TVB-2640 to quantify competitive inhibition (Ki determination).

2) Functional Genomics: CRISPR/Cas9-mediated FASN knockout in HCC cell lines to establish isogenic models for TVB-2640 response profiling.

3) Multiplex Signaling Analysis: Phosphoproteomic profiling (e.g., RPPA, Luminex) to map TVB-2640's effects on PI3K/AKT, MAPK, and UPR pathways.

4) Preclinical Efficacy: Patient-derived xenograft (PDX) models incorporating FASN-overexpressing HCC subtypes for therapeutic response correlation.

Current studies have shown that TVB-2640, in combination with paclitaxel, the disease control rate (DCR) increased from 42% in TVB-2640 monotherapy to 70%, and it could also safely combine with bevacizumab in the phase II study of relapsed high-grade astrocytoma. [7-8] These results marked the potential of future research evaluating the DCR of TVB-2640 combination with other drugs in curing HCC.

Furthermore, biomarker discovery efforts should focus on identifying predictive signatures of TVB-2640 responsiveness, such as FASN copy number variations, lipidomic profiles, or UPR activation markers. The integration of these translational approaches will accelerate the clinical deployment of FASN-targeted therapies, offering a precision medicine paradigm for HCC patients refractory to conventional treatments.

5. Conclusion

This study establishes FASN as a linchpin of HCC metabolic reprogramming and validates TVB-2640 as a domain-selective inhibitor with dual mechanisms of metabolic disruption and apoptotic induction. By bridging computational modeling with clinical correlations, we provide a robust framework for advancing FASN-targeted therapies into late-stage clinical development, addressing a critical unmet need in HCC therapeutics.

References

[1] Bicer, F. et al. (2023) 'Advances in immunotherapy for hepatocellular carcinoma (HCC)', Current Oncology, 30(11), pp. 9789–9812. doi:10.3390/curroncol30110711.

[2] Zeng H, Chen W, Zheng R, et al. Changing cancer survival in China during 2003-15: a pooled analysis of 17 population-based cancer registries [J]. The Lancet Global health, 2018, 6(5): e555-e567.

[3] Huang, J. et al. (2024) 'FASN inhibition decreases MHC-I degradation and synergizes with PD-L1 checkpoint blockade in hepatocellular carcinoma', Cancer Research, 84(6), pp. 855–871. doi: 10.1158/0008-5472.can-23-0966.

[4] Kim, D.W., Talati, C. and Kim, R. (2017) 'Hepatocellular carcinoma (HCC): Beyond sorafenib—chemotherapy', Journal of Gastrointestinal Oncology, 8(2), pp. 256–265. doi:10. 21037/ jgo.2016.09.07.

[5] Serzan, M.T. and Atkins, M.B. (2021) 'Current and emerging therapies for first line treatment of metastatic clear cell renal cell carcinoma', Journal of Cancer Metastasis and Treatment [Preprint]. doi:10.20517/2394-4722.2021.76.

[6] Fhu, C.W. and Ali, A. (2020) 'Fatty acid synthase: An emerging target in cancer', Molecules, 25(17), p. 3935. doi:10.3390/molecules25173935.

[7] Wei, W. et al. (2023) 'FBXW7β loss-of-function enhances FASN-mediated lipogenesis and promotes colorectal cancer growth', Signal Transduction and Targeted Therapy, 8(1). doi:10.1038/s41392-023-01405-8.

[8] Falchook, G. et al. (2021) 'First-in-human study of the safety, pharmacokinetics, and pharmacodynamics of first-in-class fatty acid synthase inhibitor TVB-2640 alone and with a taxane in advanced tumors', EClinicalMedicine, 34, p. 100797. doi:10. 1016/ j.eclinm.2021.100797.

[9] Kelly, W. et al. (2024) Phase II Investigation of TVB-2640 (Denifanstat) with Bevacizumab in Patients with First Relapse High-Grade Astrocytoma [Preprint]. doi:10.1158/1078-0432. c. 6637741.

[10] FASN inhibition targets multiple drivers of NASH by reducing steatosis, inflammation and fibrosis in preclinical models.

[11] TVB-2640 (FASN Inhibitor) for the Treatment of Nonalcoholic Steatohepatitis: FASCINATE-1, a Randomized, Placebo- Controlled Phase 2a Trial.

[12] Tian, L.-Y., Smit, D.J. and Jücker, M. (2023) 'The role of PI3K/AKT/mTOR signaling in hepatocellular carcinoma metabolism', International Journal of Molecular Sciences, 24(3), p. 2652. doi:10.3390/ijms24032652.

[13] Bottegoni, G. (2011) 'Protein-ligand docking', Frontiers in Bioscience, 16(1), p. 2289. doi:10.2741/3854.

[14] Zheng, L. et al. (2022) 'Improving protein–ligand docking and screening accuracies by incorporating a scoring function correction term', Briefings in Bioinformatics, 23(3). doi:10.1093/bib/bbac051.

[15] Eberhardt, J. et al. (2021) 'AutoDock Vina 1.2.0: New Docking Methods, expanded force field, and python bindings', Journal of Chemical Information and Modeling, 61(8), pp. 3891–3898. doi: 10.1021/acs.jcim.1c00203.

[16] Sung H, Ferlay J,Siegel RL,et al.Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.CA Cancer J Clin, 2021, 71 (3): 209-249.

[17] Jones, S.F. and Infante, J.R. (2015) 'Molecular pathways: Fatty acid synthase', Clinical Cancer Research, 21(24), pp. 5434–5438. doi: 10.1158/1078-0432.ccr-15-0126.