Targeting the PI3K/AKT Pathway and Fatty Acid Synthase in AL Amyloidosis: Mechanistic Insights and Therapeutic Implications

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INTRODUCTION

Systemic light chain (AL) amyloidosis is a clonal plasma cell disorder characterized by deposition of misfolded immunoglobulin light chain (LC) products in vital organs, causing their dysfunction. The molecular mechanisms underlying its pathogenesis remain incompletely elucidated. Identifying the molecular mechanisms and novel therapeutic targets is critical for improving treatment strategies and patient outcomes.

The PI3K/AKT signaling pathway is overexpressed in AL amyloidosis[1,2]. This pathway plays a critical role in regulating cellular metabolism. Specifically activated AKT can phosphorylate and regulate various target proteins involved in metabolic processes. One of the targets is fatty acid synthase (FASN), an enzyme responsible for the synthesis of fatty acids. AKT can enhance FASN expression and activity, thereby promoting lipid biosynthesis[3]. Elevated FASN levels can drive inflammation through increased fatty acid synthesis, which activates inflammatory signaling pathways and enhances cytokine production[4]. FASN overexpression has been linked to hematological malignancies and cell survival[5]. However, its role in AL amyloidosis is yet to be elucidated.

AIMS

1. To determine the role of FASN in AL amyloidosis pathology and inflammation.
2. To evaluate the therapeutic potential of targeting FASN and the PI3K/AKT pathway,

REFERENCES

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RESULTS

Figure 1.

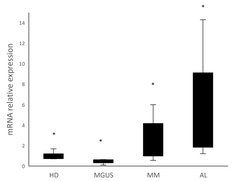

Figure 1. Upregulation of FASN in AL amyloidosis samples compared to MM, MGUS, and HCs.
FASN mRNA expression levels measured by qRT-PCR in BM-derived CD138+ cell samples of newly diagnosed patients with AL (n=15), MM (n=20), MGUS (n=8) and Healthy Controls (HC) (n=6).

Figure 2.

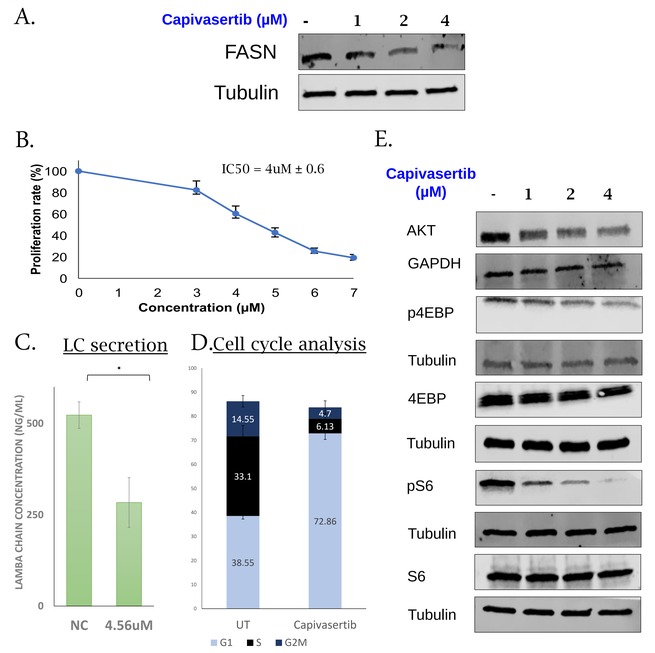

Figure 2. Targeted therapy of ALMC-1 cells with Capivasertib. **(A)** Treatment of ALMC1 cells with elevated concentrations of AKT inhibitor (Capivasertib) revealed a marked inhibition of FASN expression. Tubulin was used as a loading control. **(B)** Capivasertib treatment resulted in reduced cell proliferation, measured by WST assay, **(C)** reduced LC secretion **(D)** induced cell cycle arrest in G1 phase, and **(E)** inhibited AKT and its target genes p4EBP, pS6 as detected by western blot. Tubulin/GAPDH was used as loading control.

Figure 3.

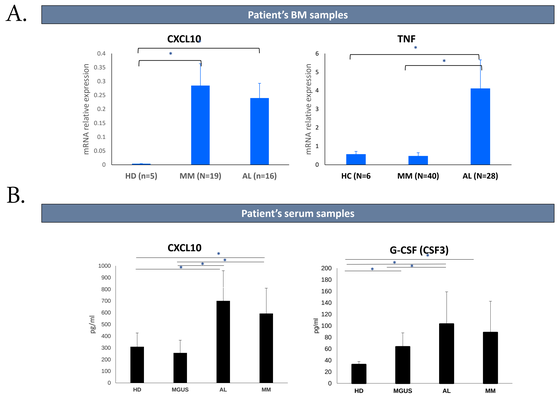

Figure 3. Proinflammatory cytokines in AL amyloidosis.
Elevated proinflammatory cytokines levels in AL amyloidosis. (A) BM and **(B)** serum samples, suggesting the involvement of the immune mechanisms.

Figure 4.

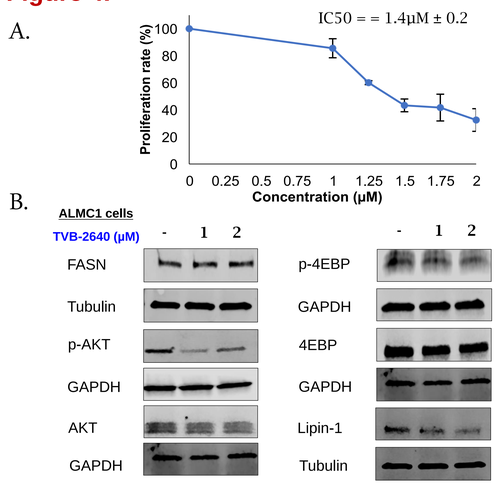

Figure 4. Targeted therapy of ALMC-1 cells with TVB-2640 (FASN inhibitor).
Treatment of ALMC-1 cells with TVB-2640 **(A)** reduced cell proliferation and **(B)** decreased the protein expression of p-AKT, p-4EBP (PI3K/AKT signalling pathway), and LIPIN-1, which is one of the key target genes regulated by FASN.

METHODS

1. FASN expression was analyzed in CD138+ bone marrow (BM) cells isolated from patients with AL amyloidosis (n=20), Multiple Myeloma (MM) (n=20), Monoclonal Gammopathy of Undetermined Significance (MGUS) (n=8), and Healthy Controls (HC) (n=6), using qRT-PCR.
2. ALMC-1 cells were treated with Capivasertib, an AKT inhibitor, to investigate the relationship between the PI3K/AKT pathway and FASN. Additionally, TVB-2640, a FASN inhibitor, was used to assess the cellular response to FASN inhibition.
3. The treatment effect was assessed as following: (a) FASN protein levels by western blot; (b) cell proliferation by WST-1 assay; (c) cell cycle by flow cytometry; (d) LC secretion by ELISA; and the expression of AKT and its downstream targets by western blot analysis.

CONCLUSIONS

Our findings highlight the significant upregulation of FASN in AL amyloidosis and its regulation by the PI3K/AKT pathway.

The observed effects of Capivasertib on FASN expression and cell proliferation, along with the upregulation of inflammatory cytokines, underscore the potential for targeting the PI3K/AKT signalling pathway and FASN in developing more specific therapeutic strategies for AL amyloidosis.

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