Suramin Suppresses Synovial Fibrosis in Osteoarthritis: Evidence of GSK3β Involvement

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INTRODUCTION: Synovial fibrosis is a hallmark of osteoarthritis (OA) progression and contributes to pain, stiffness, and joint dysfunction [1]. Aberrant activation of Wnt/β-catenin signaling drives fibroblast proliferation and extracellular matrix deposition, yet effective therapeutic strategies remain limited. GSK3β, a key regulator of Wnt activity, has been implicated in fibrotic responses, but its role in OA synovial remodeling is not fully defined. Suramin, a clinically approved drug known to modulate Wnt signaling, has not been investigated in the context of synovial fibrosis [2]. We hypothesized that suramin attenuates OA-associated synovial fibrosis through regulation of GSK3β activity.

METHODS: Animal study: After IACUC approval, OA was induced in male Sprague–Dawley rats (11 weeks old, ~400 g; n=6 per group) by anterior cruciate ligament transection (ACLT). Rats received weekly intra-articular injections of saline or suramin (0.4 mg, MedChemExpress) for 12 weeks. Contralateral knees served as controls. Synovium was harvested for histology and immunohistochemistry of COL1A1, α-SMA, and CTGF. Male rats were used to minimize variability from sex hormones. Cell culture: Human OA synovial fibroblasts (SW982 line) were treated with Wnt-3a (50 ng/mL) in the presence or absence of suramin (10 or 20 μM). Fibrosis markers (COL1A1, α-SMA, CTGF) were assessed by Western blot. Mechanistic assays: To examine the role of GSK3β and phosphorylation of GSK3β (Ser9) were analyzed by Western blot. Cells were transfected with GSK3β mutants (S9A, constitutively active; S9D, phosphorylation mimic) to validate suramin's mechanism of action. Statistics: Data are presented as mean ± SD from ≥3 independent experiments. One-way ANOVA with Tukey's post hoc test was used; $p < 0.05$ was considered significant.

RESULTS SECTION: In ACLT rats, Masson's trichrome and IHC showed that suramin significantly reduced synovial fibrosis ($p<0.001$) and decreased COL1A1, α-SMA, and CTGF staining compared with saline-treated joints ($p<0.05$–0.01, Fig.1). In SW982 fibroblasts, Western blot demonstrated that Wnt-3a markedly increased COL1A1, α-SMA, and β-catenin, whereas suramin significantly suppressed these responses ($p<0.05$, Fig.2A). Western blot densitometry further showed a dose-dependent reduction of p-GSK3β(Ser9)/GSK3β following suramin treatment ($p<0.05$, Fig.2B). To validate the mechanism, GSK3β phosphorylation mutants were used: the S9A constitutively active mutant mimicked suramin's inhibitory effects, while the S9D phosphorylation-mimic mutant abolished them, with statistically significant differences across groups ($p<0.05$–0.001, Fig.2C–D), confirming GSK3β as a key mediator of suramin's anti-fibrotic action.

DISCUSSION: Our findings demonstrate that suramin attenuates synovial fibrosis in OA by suppressing fibroblast proliferation and profibrotic marker expression. The observation that suramin inhibited GSK3β Ser9 phosphorylation together with mutant analyses showing opposing effects of S9A and S9D constructs, supports GSK3β as a key mediator of suramin's action (Fig.3). While this work highlights a potential pharmacologic approach to limit synovial fibrosis, limitations include the use of a single animal model and reliance on human synovial fibroblast cell line. In addition, suramin may exert broader chondroprotective effects beyond antifibrotic activity, which could complicate attribution of its mechanism. Further studies in additional preclinical models are warranted to clarify these effects.

SIGNIFICANCE/CLINICAL RELEVANCE: Currently, no disease-modifying therapy exists to specifically target synovial fibrosis in OA, despite its recognized role in driving pain, stiffness, and loss of joint function. Our study demonstrates that suramin reduces synovial fibrosis through modulation of GSK3β signaling. Beyond its antifibrotic actions, the pleiotropic chondroprotective effects of suramin may represent a therapeutic advantage, supporting its potential for drug repurposing. These findings highlight suramin as a candidate to address the unmet need for disease-modifying therapy in OA, as no approved treatment for synovial fibrosis currently exists.

REFERENCES: [1] Bonnevie et al. Osteoarthritis Cartilage 2025 (PMID:37866546); [2] Liu et al. Bone Joint Res. 2021 (PMID:34372688)
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IMAGES AND TABLES:

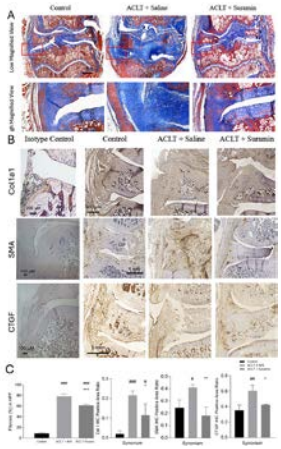

Fig. 1 Suramin reduces synovial fibrosis in vivo (A) Masson's trichrome and (B) IHC showing decreased COL1A1, α-SMA, and CTGF in ACLT rat synovium after suramin treatment. (C) Quantification of fibrosis area and IHC markers in ACLT rat synovium. $p<0.05$ vs. control (#); vs. ACLT (*)

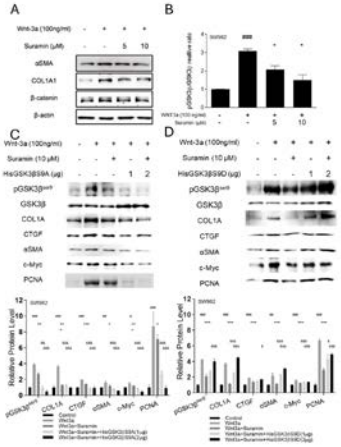

Fig. 2 Suramin suppresses profibrotic signaling in SW982 fibroblasts. (A) WB showing inhibition of Wnt3a-induced COL1A1, α-SMA, and β-catenin by suramin. (B) WB and quantification showing dose-dependent reduction of p-GSK3β/GSK3β. (C) S9A mutant mimicked, and (D) S9D mutant abrogated, suramin's inhibitory effects on fibrosis markers. $p<0.05$ vs. control (#); vs. Wnt3a (*); vs. Wnt3a+suramin (&), ANOVA with Tukey.

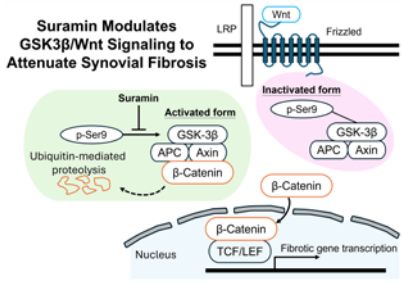

Fig. 3 Proposed mechanism of suramin action Schematic showing suramin inhibition of GSK3β Ser9 phosphorylation, β-catenin degradation, and reduced fibrotic gene transcription.