MEDICAL UNIVERSITY OF VIENNA

The urokinase inhibitor BC11 attenuates skin fibrosis via macrophage-fibroblast crosstalk modulation

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Background & Methods

Fibrotic diseases are characterized by persistent inflammation and excessive extracellular matrix deposition, ultimately leading to progressive tissue remodeling and organ dysfunction. Despite increasing insight into fibrotic mechanisms, effective antifibrotic treatment options remain limited. Here, we investigated the anti-inflammatory and antifibrotic effects of BC11, a selective urokinase inhibitor, with a particular focus on fibroblast and macrophage responses and their contribution to fibrotic remodeling.

BC11 was studied using single-cell RNA sequencing of murine scars, primary human dermal fibroblasts, cytokine and extracellular matrix protein analyses, and functional monocyte-migration assays. Translational effects were further assessed in ex vivo human skin and fibrotic lung tissue.

Results

BC11 remodels the cellular composition of murine scars

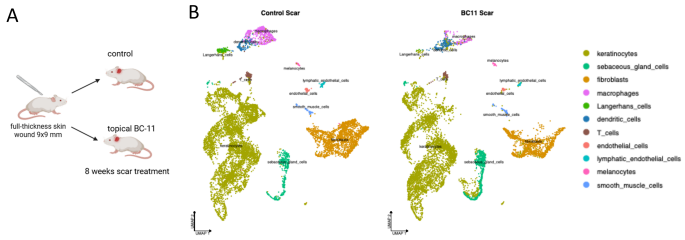


Figure 1: Cellular Landscape. **(A)** Experimental setup: full-thickness skin wounds were treated with topical BC11 for 8 weeks. **(B)** UMAP plots show reduced macrophage and fibroblast abundance in BC11 treated tissue compared to control, indicating a shift in cellular composition.

Reduction of macrophage population & inflammation

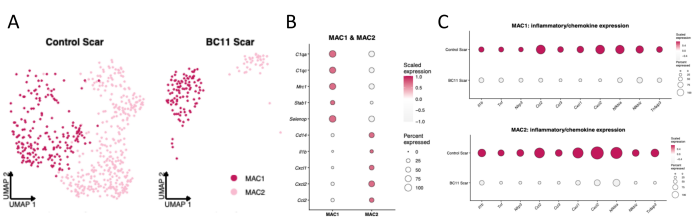
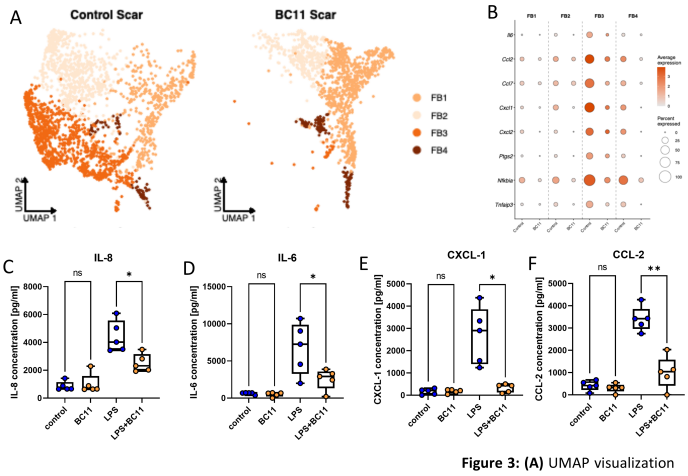


Figure 2: (A) UMAP visualization of macrophage states in control and BC11-treated scars. **(B)** Expression of marker genes characterizing macrophage states MAC1 and MAC2. **(C)** Expression of selected inflammatory and chemotactic genes across macrophage states in control and BC11-treated scars.

BC11 shifts fibroblast-state composition and attenuates inflammatory fibroblast programs



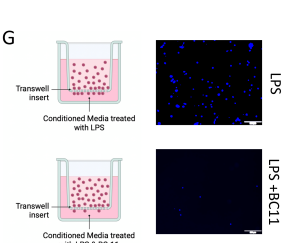


Figure 3: (A) UMAP visualization of fibroblast states FB1–FB4 in control and BC11-treated scars. **(B)** Expression of selected marker genes characterizing fibroblast states. **(C–F)** IL-8 **(C)**, IL-6 **(D)**, CXCL1 **(E)**, and CCL2 **(F)** concentrations in supernatants of primary human dermal fibroblasts treated with LPS with or without BC11. **(G)** Transwell migration assay using fibroblast-conditioned medium, showing reduced monocyte migration following BC11 treatment.

BC11 suppresses NF-κB-associated inflammatory signaling

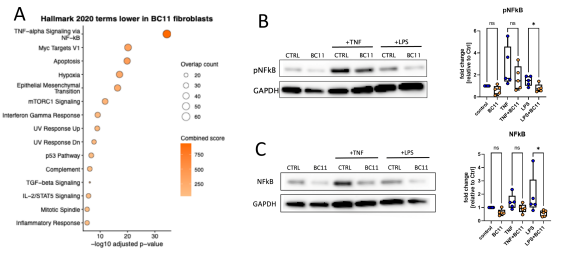


Figure 4: **(A)** Hallmark pathway enrichment analysis of genes expressed at lower levels in BC11-treated scar fibroblasts. **(B, C)** Representative immunoblots and densitometric quantification of phosphorylated NF-κB p65 **(B)** and total NF-κB p65 **(C)** in primary human dermal fibroblasts under the indicated treatment conditions.

BC11 suppresses fibroblast activation and YAP-associated profibrotic programs

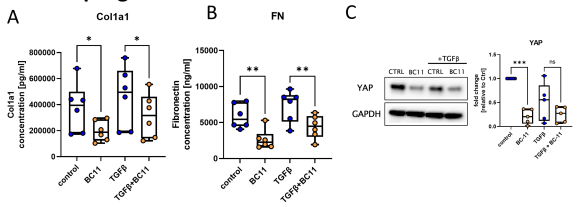


Figure 5: COL1A1 **(A)** and fibronectin **(B)** concentrations in supernatants of primary human dermal fibroblasts cultured under basal or TGF-β-stimulated conditions with or without BC11. **(C)** Representative YAP immunoblot and densitometric quantification showing reduced YAP abundance following BC11 treatment.

BC11 suppresses inflammatory and profibrotic responses in human skin ex vivo

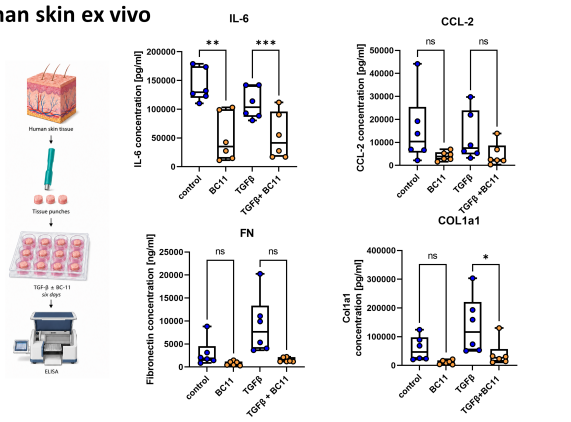


Figure 6: (A) Experimental workflow for ex vivo culture of human skin tissue punches. **(B–E)** IL-6 **(B)**, CCL2 **(C)**, fibronectin **(D)**, and COL1A1 **(E)** concentrations in culture supernatants after 6 days of treatment with BC11, TGF-β, or their combination

BC11 attenuates inflammatory and fibrotic responses in human fibrotic lung tissue ex vivo

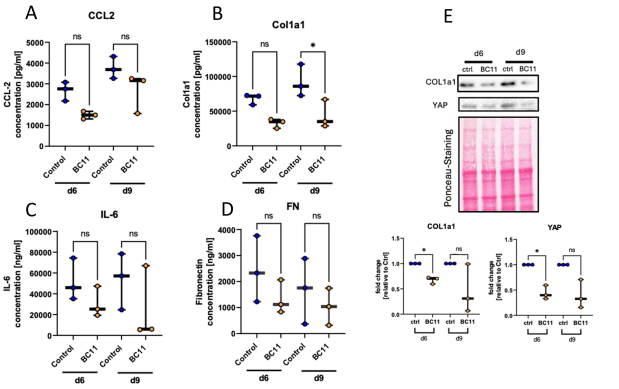


Figure 7: CCL2 (A), COL1A1 (B), IL-6 (C), and fibronectin (D) concentrations in supernatants of human fibrotic lung tissue cultured with or without BC11 for 6 or 9 days. (E) Representative immunoblots and densitometric quantification of COL1A1 and YAP in tissue lysates.

Conclusion

BC11 remodels macrophage- and fibroblast-driven inflammatory programs and attenuates profibrotic signaling and extracellular matrix production. These effects extend to human skin and fibrotic lung tissue ex vivo, supporting BC11 as a potential therapeutic strategy for fibrotic disease.

All authors declare no conflict of interest.