Seladelpar Downregulates Inflammatory and Fibrotic Pathways: Insights From Serum Proteomic Analysis

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Conclusions

- Unbiased pathway analyses of serum proteomic changes with seladelpar treatment indicated inhibition of pathways related to inflammation/immune activation, fibrosis/tissue remodeling, together with activation of selected peroxisome proliferator–activated receptor (PPAR) signaling and metabolic pathways
- These analyses expand on previously reported seladelpar-mediated reduction in serum proteins associated with cholestasis, pruritus, fibrosis, and inflammation as well as increases in known targets of PPARδ involved in lipid metabolism[1]
- In addition to the well-established anticholestatic and antipruritic effects of seladelpar in primary biliary cholangitis, these data provide biological context for the reductions in liver injury markers, inflammation markers, and stabilization or improvement in liver stiffness with seladelpar treatment

Plain Language Summary

- In this study, researchers examined changes in proteins in the blood from patients with primary biliary cholangitis who received seladelpar treatment in the Phase 3 RESPONSE clinical trial
- Over 12 months of seladelpar treatment, there were improvements in protein levels related to liver health, inflammation, and scarring
- These findings provide additional information about the biological processes that may contribute to the effects of seladelpar

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Introduction

- Primary biliary cholangitis (PBC) is a chronic, autoimmune, cholestatic liver disease that disproportionately affects women and is associated with progressive liver injury and significant symptom burden[2]
- Seladelpar is a first-in-class delpar (selective peroxisome proliferator–activated receptor delta [PPARδ] agonist) indicated for the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as monotherapy in patients who are unable to tolerate UDCA[3-5]
- In the pivotal RESPONSE study (NCT04620733), seladelpar led to significantly more patients achieving the primary endpoint of a composite biochemical response based on alkaline phophatase (ALP) and total bilirubin than placebo
  - Seladelpar significantly improved markers of cholestasis (ALP, gamma-glutamyl transferase [GGT], and bile acids), inflammation (immunoglobulin M [IgM], C-reactive protein [CRP]), and led to improvement in pruritus[6]
- Liver stiffness was stable or improved in most patients receiving seladelpar over 3 years[7-9]
- Previous proteomic analyses of the RESPONSE study showed that seladelpar treatment led to reductions in serum proteins associated with cholestasis, pruritus, and fibrosis biomarkers at baseline and increases in serum levels of canonical PPARδ targets[1]
- Here, we present an expanded proteomic analysis of the RESPONSE study[6]

Objectives

- To characterize longitudinal changes in the serum proteome associated with seladelpar treatment using highly sensitive proteomic profiling with SomaScan®
- To identify key biological processes modulated by seladelpar using unbiased pathway analysis of treatment-associated serum proteomic changes

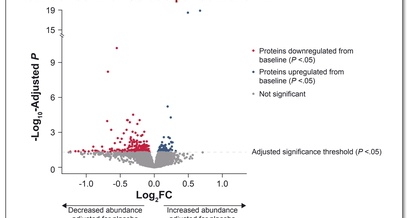
Methods

- In the RESPONSE study, 193 patients with PBC were randomized 2:1 to receive placebo or seladelpar 10 mg for 12 months[6]
- Serum proteomes from 180 patients (862 samples) were profiled using the SomaScan® 11k Assay version 5.0, which quantifies 9852 human proteins
  - Data normalization, calibration, and quality control processes were performed according to the manufacturer's instructions[10]
- Changes in protein levels were analyzed using mixed-effects models that estimated placebo-adjusted changes from baseline with treatment, time, treatment-time interaction, age, sex, baseline disease severity, and plate ID treated as fixed effects, and patients treated as random effects
  - For visualization purposes, the same model was also applied separately within the seladelpar and placebo treatment groups at Months 1, 3, 6, and 12
- To identify pathways modified by seladelpar, the full SomaScan® dataset comprising 9,634 valid and unique serum protein targets, together with corresponding $\log_2$FC and *P*-values, was uploaded to Ingenuity Pathway Analysis (IPA; Qiagen); a core analysis in IPA was performed using proteins that showed significant placebo-adjusted changes from baseline at Month 12 (P <.05 and absolute $\log_2$FC >.25) in patients who achieved the composite biochemical response previously described in the RESPONSE study (ALP <1.67 × upper limit of normal [ULN], total bilirubin ≤1 × ULN, and ALP reduction ≥15% from baseline)[6]
- Canonical pathways were considered significantly modulated if they met the Benjamini-Hochberg–adjusted significance threshold (adjusted P <.05) and had an absolute activation z-score >1.5, with positive z-scores indicating predicted activation and negative z-scores predicted inhibition; significant pathways were then grouped by biological process based on literature

Results

- Seladelpar treatment resulted in significant changes in the serum proteome over time
- At Month 12, 339 serum proteins were significantly modified in patients who achieved the composite biochemical response; 100 proteins were upregulated and 239 proteins were downregulated (adjusted P <.05; **Figure 1**)

Figure 1. Placebo-Adjusted Changes in Serum Protein Abundance With Seladelpar at Month 12[a]

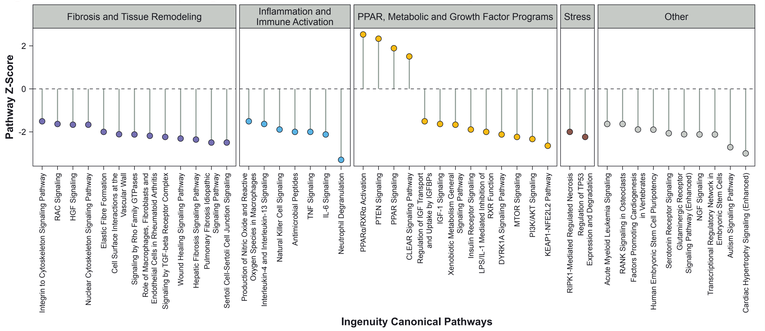


[a]In patients who achieved the composite biochemical response.
FC, fold change.

Results

- Unbiased IPA identified canonical pathways significantly modulated by seladelpar (**Figure 2**)
- The key modulated pathways were grouped into biological processes including
  - Fibrosis and tissue remodeling
  - Inflammation and immune activation
  - PPAR signaling, metabolic, and growth factor programs
- Pathways associated with inflammatory and fibrotic processes were predicted to be inhibited by seladelpar treatment while PPAR signaling pathways were predicted to be upregulated (**Figure 2**)

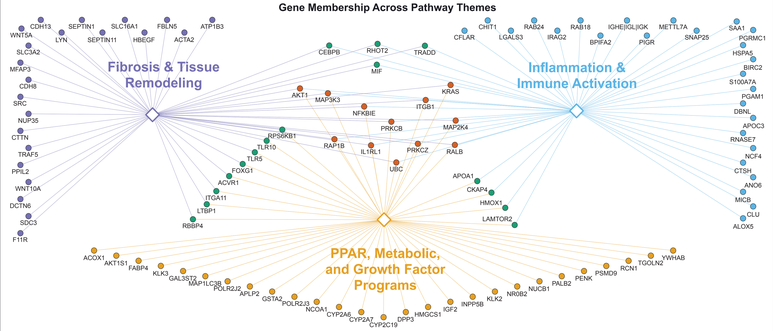
Figure 2. Canonical Pathways Significantly Altered in Serum Proteome by Seladelpar Treatment at Month 12



Canonical pathways identified by IPA that met the Benjamini-Hochberg–adjusted significance threshold (P <.05) and an absolute activation z-score >1.5 are shown and grouped by biological process. Each point represents a canonical pathway z-score (positive = predicted activation, negative = predicted inhibition). Biological processes were assigned based on literature.
IPA, Ingenuity Pathway Analysis; PPAR, peroxisome proliferator–activated receptor.

- The modified proteins included 46 proteins annotated to fibrosis and tissue remodeling, 46 proteins to inflammation and immune activation, and 51 proteins to metabolism; some proteins were represented in more than 1 biological process (**Figure 3**)

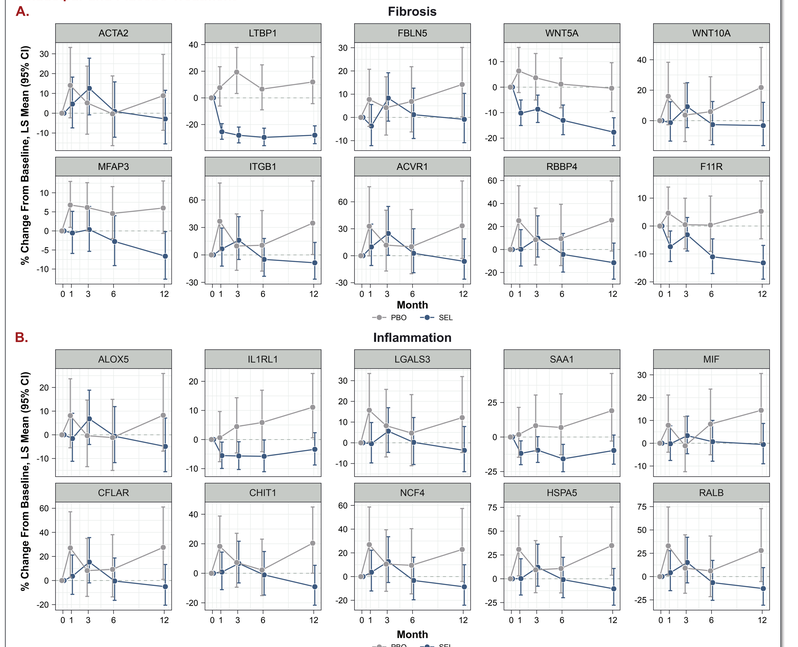
Figure 3. Serum Proteins Modified by Seladelpar Treatment Belong to Three Main Biological Processes: Fibrosis, Inflammation, and Metabolism



The network includes proteins annotated to at least one canonical pathway within the fibrosis and tissue remodeling, inflammation and immune activation, or metabolism biological processes. Nodes represent proteins and are colored by biological process; edges connect proteins that share membership in at least 1 canonical pathway within indicated biological processes.
PPAR, peroxisome proliferator–activated receptor.

- Longitudinal changes in selected proteins associated with fibrosis and tissue remodeling or inflammation and immune activation are shown in **Figure 4**
- Compared with placebo, seladelpar was associated with reductions in the abundance of selected fibrosis- and tissue remodeling–associated proteins (**Figure 4A**) and inflammation- and immune activation–associated proteins (**Figure 4B**)
- The separation between treatment groups was generally greatest at Month 12, indicating that seladelpar-associated changes in serum proteins associated with fibrotic and inflammatory processes increased and were sustained over time

Figure 4. Longitudinal Changes in Selected (A) Fibrosis- and (B) Inflammation-Associated Serum Proteins With Seladelpar and Placebo Treatment



LS mean percentage changes from baseline with 95% confidence intervals are shown through Month 12 for seladelpar and placebo. In panel A, selected proteins associated with fibrosis and tissue remodeling are shown. In panel B, selected proteins associated with inflammation and immune activation are shown. The horizontal dashed line indicates no change from baseline.
ACTA2, alpha-2 actin; ACVR1, activin receptor type-1; ALOX5, arachidonate 5-lipoxygenase; CFLAR, caspase-8 and FADD-like apoptosis regulator; CHIT1, chitinase 1; FADD, Fas-associated protein with a death domain; FBLN5, fibulin-5; F11R, F11 receptor; HSPA5, heat shock protein family A member 5; IL1RL1, interleukin 1 receptor-like 1; ITGB1, Integrin Subunit Beta 1; LGALS3, galectin-3; LS, least-squares; LTBP1, latent TGFβ binding protein 1; MFAP3, microfibril-associated glycoprotein 3; MIF, macrophage migration inhibitory factor; NCF4, neutrophil cytosolic factor 4; PBO, placebo; RALB, ras-related protein Ral-B; RBBP4, retinoblastoma-binding protein 4; SAA1, serum amyloid A1; SEL, seladelpar; WNT5A, Wnt family member 5A; WNT10A, Wnt family member 10A.

Limitations

- SomaScan® analysis identified potential novel circulating biomarkers reflective of PBC disease severity and markers indicative of PPARδ pathway engagement
- This exploratory proteomic analysis was based on circulating protein abundance and does not directly establish changes in hepatic tissue pathways or causal mechanisms; these novel markers require further validation against other platforms and with long-term patient data
- Interpretation of IPA results is constrained by pathway annotation depth and literature coverage; symptom-based complex clinical manifestations such as fatigue and pruritus may be incompletely captured
  - The only pruritus related pathway in IPA canonical pathway database, serotonin receptor signaling, was downregulated by seladelpar treatment