Serum proteomics reveals association of CCL24 with key aspects of Primary Sclerosing Cholangitis

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Introduction
Primary Sclerosing Cholangitis (PSC) is a chronic liver disease that is marked by the presence of a damaged peribiliary space. The pro-fibrotic chemokine CCL24 has been implicated in driving these self-reinforcing mechanisms in fibrotic-inflammatory diseases (1-2). CCL24 is overexpressed in livers of patients with primary sclerosing cholangitis (PSC), predominantly in areas of evident biliary injury.

We previously showed that CCL24 blockade, using a monoclonal antibody, interferes with core pathways that induce PSC pathophysiology in pre-clinical models (3).

Aim
To demonstrate the role of CCL24 in PSC and its association with disease related pathways, we analyzed the serum proteome in healthy control and patients with PSC. CCL24's association with key aspects of PSC was examined by:

1. Correlation of serum CCL24 with inflammation, fibrosis and vascularization-related proteins.
2. Exploring pathways enriched in patients with high CCL24 serum levels.
3. Characterization of CCL24 dependent protein signature in hepatic stellate cell line, and assessment of this protein signature in healthy vs patients' sera.

Method
Sera from healthy controls (n = 30) and patients with PSC (n = 45) were analyzed using the Olink proximity extension assay (PEA) of 3072 proteins. We focused on extracellular proteins by extracting 991 intracellular proteins. Individuals' demographics, enhanced liver fibrosis (ELF) scores and alkaline phosphatase (ALP) levels were documented. Differentially expressed proteins (DEPs; p<0.05 by Welch two sample t-test) were submitted to pathway analysis using Ingenuity Pathway Analysis (IPA). To evaluate the direct effect of CCL24 on hepatic cells, an LX2 hepatic stellate cell (HSC) line was stimulated with CCL24 and subsequently blocked by a neutralizing monoclonal antibody (CM CCL24).

Conclusions
CCL24 is associated with PSC-related pathways and severity. A CCL24 related signature in hepatic stellate cells differentiates patients with PSC from healthy controls and by disease severity.

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