Crosslinking Proteomics Reveals the AKAP12–PKA Axis in Lipid Homeostasis During Alcohol-Associated Liver Disease

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Our role: Creative Proteomics performed crosslinking proteomics combined with high-resolution Nano LC-MS/MS analysis, supporting AKAP12-centered interactome discovery and helping reveal the AKAP12–PKA lipid-regulatory axis in alcohol-associated liver disease.

Background & Significance

Alcohol-associated liver disease is characterized by disrupted lipid homeostasis and progressive hepatic steatosis. Although PKA signaling is known to suppress lipogenesis and support fatty acid oxidation, the scaffold mechanisms organizing this protective pathway remain unclear. AKAP12, a PKA-anchoring protein, was investigated as a potential regulator of alcohol-induced metabolic imbalance.

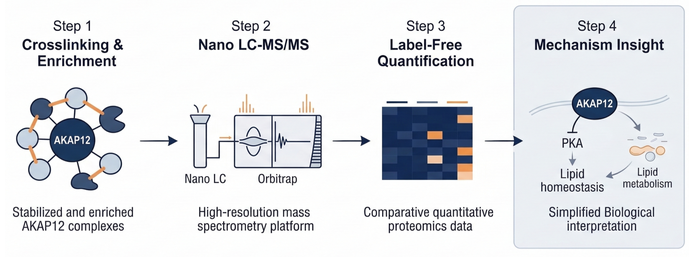
Scientific Challenge

This study required more than conventional expression-level analysis. The key question was whether alcohol exposure alters AKAP12-associated protein interactions in a way that rewires lipid-regulatory signaling. Addressing this mechanism demanded an interaction-focused proteomics workflow capable of capturing AKAP12-centered complexes and linking them to metabolic dysfunction.

Study Objective

To determine how the AKAP12–PKA signaling axis regulates lipid homeostasis during alcohol-associated liver disease, and whether disruption of AKAP12-centered protein interactions contributes to triglyceride accumulation and hepatic steatosis.

Workflow (Bind → Verify → Function)



This workflow enabled AKAP12-centered interactome discovery through crosslinking proteomics, Nano LC-MS/MS analysis, and label-free quantification, supporting downstream interpretation of PKA-linked lipid homeostasis in ALD.

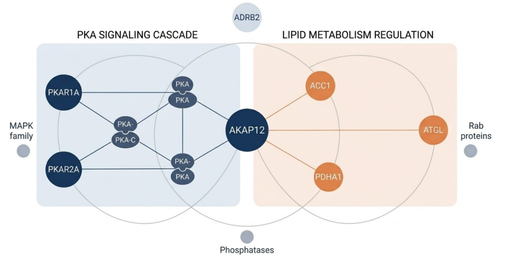
Contact Us

Web: www.creative-proteomics.com

Key Findings & Impact

Crosslinking proteomics identified the AKAP12 interactome

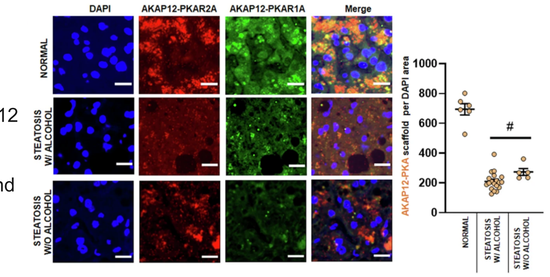
Crosslinking proteomics revealed that AKAP12 associates with PKA-related components and multiple lipid-regulatory proteins. Key interacting partners included proteins involved in signaling and metabolic control, supporting AKAP12 as a scaffold linking PKA activity to hepatic lipid homeostasis.



Schematic interaction network based on crosslinking proteomics findings, highlighting AKAP12-associated signaling and lipid-regulatory partners relevant to hepatic lipid homeostasis.

Alcohol exposure disrupts AKAP12-associated signaling complexes

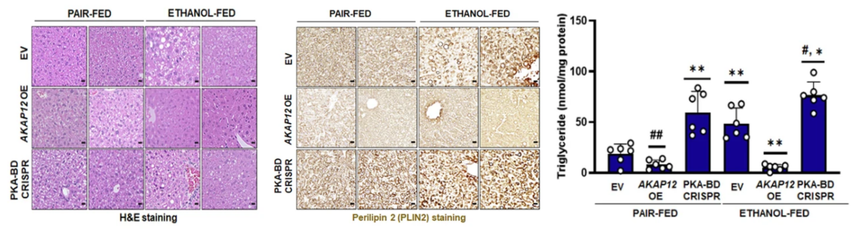
Alcohol exposure weakened AKAP12 interaction with PKA regulatory subunits and with lipid-regulatory partners including ACC1, PDHA, and ATGL. These results indicate that alcohol remodels the AKAP12 scaffold and compromises the signaling architecture required for metabolic protection.



Alcohol exposure diminished AKAP12 interaction with PKA regulatory subunits, supporting disease-associated disruption of a protective signaling scaffold.

Disruption of the AKAP12–PKA axis promotes steatosis

Functional studies showed that perturbation of the AKAP12–PKA scaffold promoted lipid accumulation in ALD models. In mouse liver, AKAP12 modulation altered PLIN2 staining, BODIPY lipid staining, triglyceride content, and downstream PKA-linked metabolic signaling, linking interaction loss to steatotic phenotype.



Functional studies showed that perturbation of the AKAP12-PKA scaffold promoted lipid accumulation in ALD models.

Our Contribution (Creative Proteomics)

Creative Proteomics performed **crosslinking proteomics combined with high-resolution Nano LC-MS/MS analysis** to characterize AKAP12-associated protein complexes and support mechanistic insights interpretation in ALD. Samples were analyzed on an Ultimate 3000 nano UHPLC-Q Exactive HF platform, enabling AKAP12-centered interactome discovery and downstream biological validation.

What Problems We Help Solve

- Identify target-centered protein interaction networks
- Detect condition-dependent changes in protein interaction networks
- Reveal signaling partners linked to disease phenotypes
- Support mechanism-focused interpretation beyond abundance analysis

This study is a representative example: crosslinking proteomics identified AKAP12-associated signaling and lipid-regulatory partners, while downstream validation linked interaction changes to disrupted PKA signaling and steatosis.

Why Choose Creative Proteomics

- High-resolution Orbitrap platform with up to 240,000 resolving power at m/z 200
- Low-ppm mass accuracy with instrument specifications of 3 ppm external calibration (24 h) and 1 ppm internal calibration
- Sensitive analysis of complex interaction samples for crosslinking proteomics and mechanism-focused studies
- Standardized QC review across acquisition, data processing, and result delivery
- End-to-end workflows supporting publication-ready outputs and downstream biological interpretation

Need to uncover protein interaction networks in your disease model?

Creative Proteomics combines crosslinking proteomics, Nano LC-MS/MS, and quantitative analysis to support protein interaction discovery and downstream biological interpretation.

Contact us to discuss a customized workflow for your next proteomics project.

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