Pathogenesis and management of Colorectal Neoplasia in PSC-Associated Colitis

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Background

- Patients with PSC-IBD face a 4–5× increased colorectal neoplasia (CRN) risk compared with IBD alone, with right-sided, flat, multifocal lesions and accelerated progression.
- Recent data showed PSC colonic mucosa harbors a distinct right-colon, adaptive inflammatory program (I2 state), enriched for antigen-driven responses and IL-17^{+}FOXP3^{+} double-positive CD4 T cells, which predict shorter time to dysplasia.
- Conjugated bile acids (e.g., TUDCA, TCDCA) destabilize FOXP3^{+} Tregs via S1PR → DNMT/STAT3 signaling, shifting towards pathogenic Th17-like states.
- Etrasimod (S1PR1/4/5 modulator, approved for UC) alters colonic immune composition, offering a translational probe of these pathways.
- **Clinical need:** No biomarkers available to stratify PSC-IBD surveillance.

Overall Aim

To define clinically meaningful, tissue-based predictors and mechanisms of CRN in PSC-associated IBD by integrating:

1. Registry-level data
2. FFPE-compatible transcriptomic/spatial profiling of archived pre-dysplasia colon biopsies, and
3. Exploratory mechanistic modeling of bile-acid–driven T-cell plasticity and therapeutic modulation by S1PR agonists (etrasimod).

Central Hypothesis

CRC risk in PSC-IBD arises from a distinct immune–metabolic program where bile acids promote IL-17/FOXP3 plasticity to create carcinogenic niches. These features are measurable in pre-dysplasia biopsies and modifiable via S1PR modulation.