**Probing the Structural Basis of Triclosan-Glucuronide Processing by Flavin Mononucleotide-Binding β-Glucuronidases**

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**Background**

Inflammatory bowel disease (IBD) impacts 5 million people globally. It is estimated that nearly 2 million Americans have IBD, and that the United States spends up to $32 billion annually on IBD care. The origins of IBD are unknown; however, there are some well-established risk factors. These include immune system malfunctions, exposure to antibiotics and nonsteroidal anti-inflammatory medications, genetic predisposition, and environmental risk factors such as triclosan. Triclosan is a commonly used anti-microbial agent that can be found in hand soaps, children's toys, toothpaste, and cosmetics. In its native form, triclosan is an IBD risk factor. In the liver, triclosan undergoes phase II metabolism and is appended with a glucuronic acid moiety. The triclosan-glucuronide is sent to the bowel where the glucuronic acid moiety is cleaved by bacterial β-glucuronidases. This restores triclosan to its native form which can cause irritation to the lining of the bowel.

**CONSUMER PRODUCTS**

**PLASMA**

**LIVER**

Triclosan

Glucuronic acid

Medications,

and loop agent

**GUS**

**Resorption by bacterial β-glucuronidase**

**GUS**

**Phase II Metabolism:** Glucuronidation by UGTs

**IBD Information**

Figure 5: Triclosan metabolism and resorption pathway within the human body.

**Results**

**Figure 8**

**Figure 9**: Broad screening of a panel of GUS from all loop classes using UDH/NAD⁺ coupled assay.

**Figure 10**: Loop 1 and FMN-binding GUS TCS processing efficiency.

**Figure 11**: Panel of GUS that process TCS efficiently. (TCS ligand in dark blue, hypothesized key residues in cyan, catalytic glutamates in gray)

**Figure 12**: Draft screening of a panel of GUS from all loop classes using UDH/NAD⁺ coupled assay.

**Figure 13**: Loop 1 and FMN-binding GUS TCS processing efficiency.

**Figure 14**: Panel of GUS that process TCS efficiently. (TCS ligand in dark blue, hypothesized key residues in cyan, catalytic glutamates in gray)

**Figure 15**: The flavin-binding GUS, UNC X: hypothesized key residues identified via site-directed mutagenesis. Two residues in the C-terminal domain were found to be significant in TCS processing ability. Mutations to these residues increased processing efficiency.

**Figure 16**: The Loop 1 GUS, UNC X: Hypothesized key residues identified via site-directed mutagenesis. Two residues were found to be significant in TCS processing ability. Mutations to these residues increased processing efficiency.

**GUS Mutant**

**GUS Mutant**

**GUS Mutant**

**Methods**

**TCS GUS processing**

**Catalytic efficiency**

**Design of mutants to determine significance**

**Hypothetical key residues of interest based on aromatic interactions and proximity**

**Conclusions**

- Loop 1 and FMN-binding GUS significant
- Most successful processors of environmental risk factor Triclosan
- Structural modeling and tests indicate:
  - Specific active site residues significant
  - Aromatic interaction
  - Minimal congestion of active site
  - Favorable amino acid characteristics

**Figure 17**: Overview of the methodology for testing GUS TCS processing ability.

**Figure 18**: The main types of IBD and location in bowel

**Future Directions**

- **References**


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7. Mayneoff inflammatory bowel Disease Center, Johns Hopkins University, About IBD: Colon Disease and Ulcerative Colitis.