

Title: An unexplored mechanism of antimicrobial resistance: gut microbial modification of antibiotics by sulfation

Seed idea description

The gut microbiome is known to play an important role in drug metabolism, yet its potential to chemically modify antibiotics and thereby alter their antimicrobial activity remains poorly understood. We propose to investigate whether gut microbial sulfotransferases can sulfate antibiotics and alter their potency, bioavailability, or susceptibility to bacterial resistance mechanisms.

Gut microbes encode aryl-sulfate sulfotransferases (ASSTs), that can transfer sulfo groups to structurally diverse phenolic molecules. Our recent work demonstrates broad substrate promiscuity of a gut microbial ASST toward host, dietary, and pharmaceutical derived compounds. Interestingly, earlier studies showed that some bacterial sulfotransferases can sulfate certain antibiotics, but the broader significance of this chemistry for antibiotic activity and antimicrobial resistance have not been investigated.

We hypothesize that gut microbial sulfotransferases can potentially modify susceptible antibiotics and alter their antimicrobial activity. We will identify antibiotic substrates of representative gut microbial sulfotransferases, characterize antibiotic sulfation using biochemical and mass-spectrometric approaches, and determine whether sulfation changes antibiotic activity using bacterial growth and susceptibility assays. In addition, we will investigate if sulfotransferase expressing gut bacteria alter antibiotic efficacy within microbial communities. To understand the broader metabolic impact of ASSTs, we will develop an AI-assisted structure-function approach to predict their substrate specificity and identify potential substrates.

This work could uncover a previously unknown mechanism through which the gut microbiome influences antibiotic exposure and activity, establishing a mechanistic connection between microbial drug metabolism and antimicrobial resistance.

Anticipated deliverables

Identification of antibiotics that are substrates for gut microbial sulfotransferases, determination of how sulfation affects antimicrobial activity, identification of sulfotransferase genes or microbial taxa with the potential to influence antibiotic efficacy, preliminary data supporting external grant applications, and a manuscript describing gut microbial sulfation as a potential mechanism influencing antibiotic activity and antimicrobial resistance.

Direct policy implications, if any

Understanding whether gut microbial metabolism alters antibiotic efficacy could inform strategies for optimizing antimicrobial use and help explain interindividual variation in

antibiotic response. In the longer term, microbial drug-metabolism markers could potentially contribute to more personalized selection or dosing of antimicrobial therapies.

Disciplines/expertise required

Biostatistics - For statistical analysis and integration of high-dimensional datasets

Microbial ecology - Help with microbial community dynamics due to antibiotic modification

Evolutionary biology - To help understand evolution and distribution of microbial sulfotransferases and antimicrobial resistance

Mathematical modeling - To help develop quantitative models to predict gut microbial sulfotransferases mediated antibiotic modification and resistance at a community level

Data Science / Machine Learning - Expertise in developing machine-learning approaches to predict ASST substrate specificity and potential antibiotic-enzyme interactions