Thioglycosides Modulate Bacterial Glycosylation
Isabella Quintana, 2023

Increasing antibiotic resistance in the last decade has resulted in a pressing need for new, selective therapies. *Helicobacter pylori* is a prime example of a multi-drug resistant pathogen, which has infected about 50% of the global population.[1] The glycans that coat the surface of bacteria are compelling therapeutic targets because they contain distinct monosaccharides that are absent from human cells and are linked to pathogenesis. As such, disrupting the synthesis of fully functional glycans presents a possible pathway of inhibiting a bacteria's ability to infect the host. The Dube lab previously demonstrated O-glycoside inhibitors based on rare bacterial monosaccharides to be effective in disrupting glycan biosynthesis in *H. pylori*. A recent study by Wang *et al.* established in mammalian systems that a novel class of metabolic inhibitors, thioglycosides (S-glycosides), were effective at >10-fold lower concentrations than O-glycosides due to their increased stability in cells.

This project assessed a panel of three S-glycosides based on rare bacterial monosaccharides for their ability to truncate glycan biosynthesis and elicit fitness defects via western blot analysis and fitness assays, respectively. These compounds were screened in the pathogenic bacteria *H. pylori*, the commensal gut organism *B. fragilis*, and mammalian cells. The S-glycosides altered glycan biosynthesis and affected bacterial fitness in *H. pylori* but not in *B. fragilis.* The inhibitors did not impact mammalian cell glycosylation or growth. These findings suggest selectivity of inhibitors for pathogenic bacteria. Results demonstrate S-glycosides are effective at comparable concentrations to O-glycosides. Ultimately, selectively targeting bacterial pathogens through their unique glycans has the potential to expand our antibiotic arsenal.

Figures

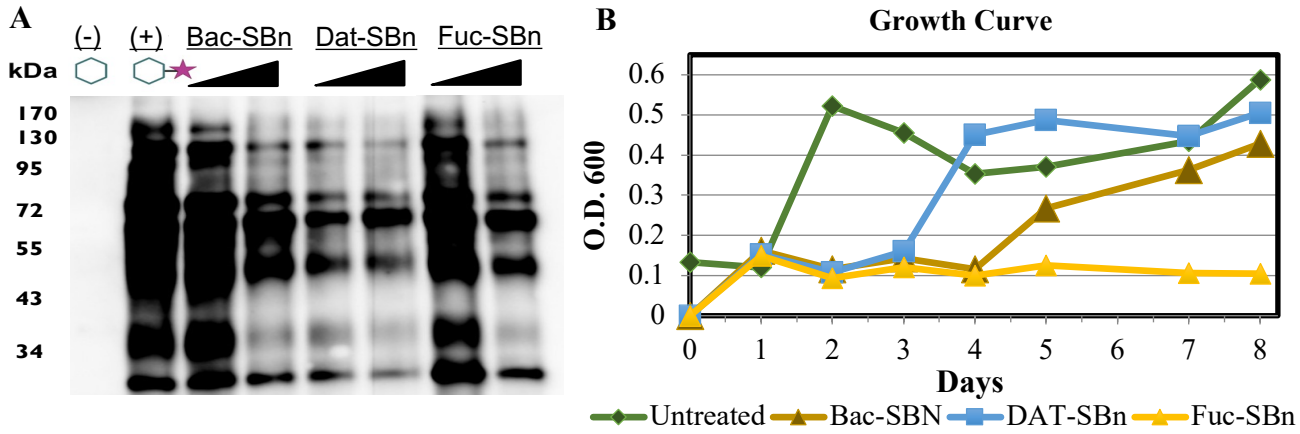

Figure 1. S-glycosides impact glycan biosynthesis and bacterial fitness in a compound dependent manner in *H. pylori*. (A) Bacteria were grown in the presence of an azide tag and 1-2 mM of an inhibitor for 4 days. Western blotting using an anti-FLAG antibody was utilized to detect the azide-labeled glycoproteins in *H. pylori*. Bac-SBn and Fuc-SBn caused a significant reduction in glycan biosynthesis at the higher inhibitor concentration (2 mM), while DAT-SBn demonstrated inhibition starting at 1 mM. (B) To measure growth, bacteria were inoculated in liquid culture and incubated in microaerophilic conditions. The OD_{600} of each culture was measured over the course of 8 days. Fuc-SBn was the only inhibitor that caused a reduction in growth compared to untreated bacteria.

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References

1. Frieri, M.; Kumar, K.; Boutin, A. Antibiotic resistance. *Journal of Infection and Public Health* 2017, *10* (4), 369-378