

A human milk oligosaccharide, 2'-fucosyllactose (2'-FL), protects intestinal mucosal integrity through regulation of gut microbial metabolism

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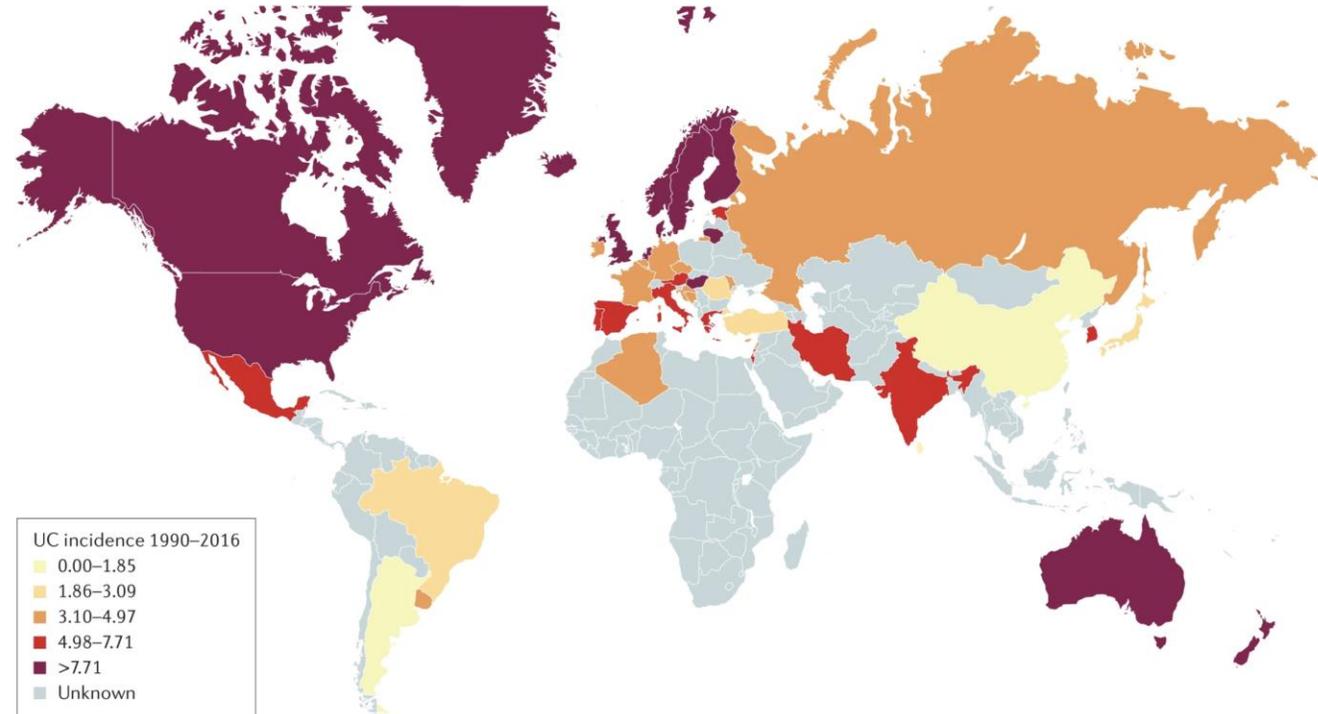


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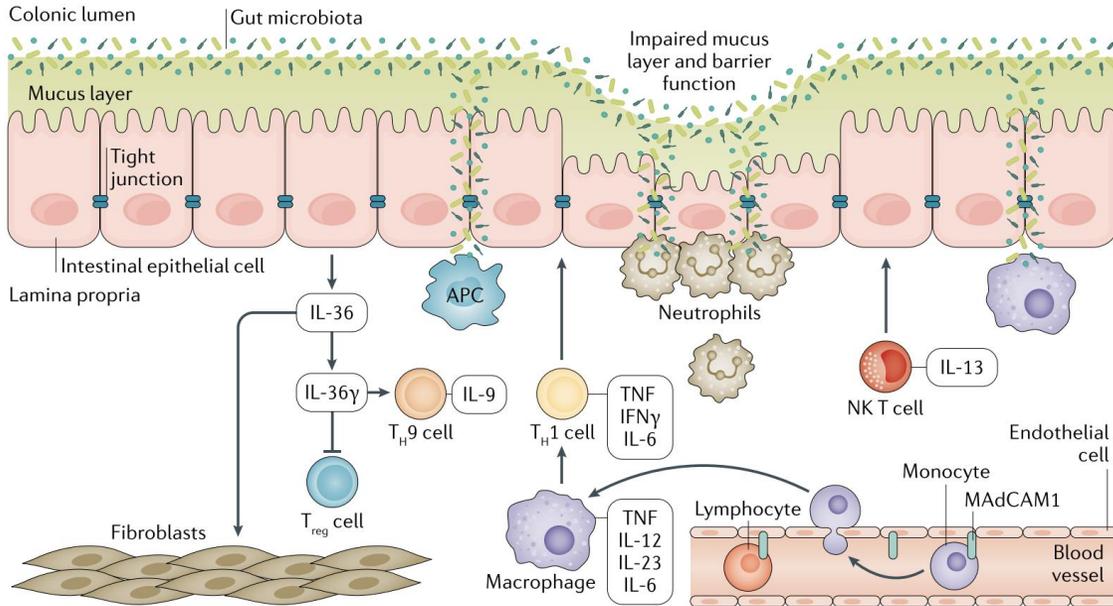
Schalich, et al., mBio, 2024

Prevalence of ulcerative colitis (UC)

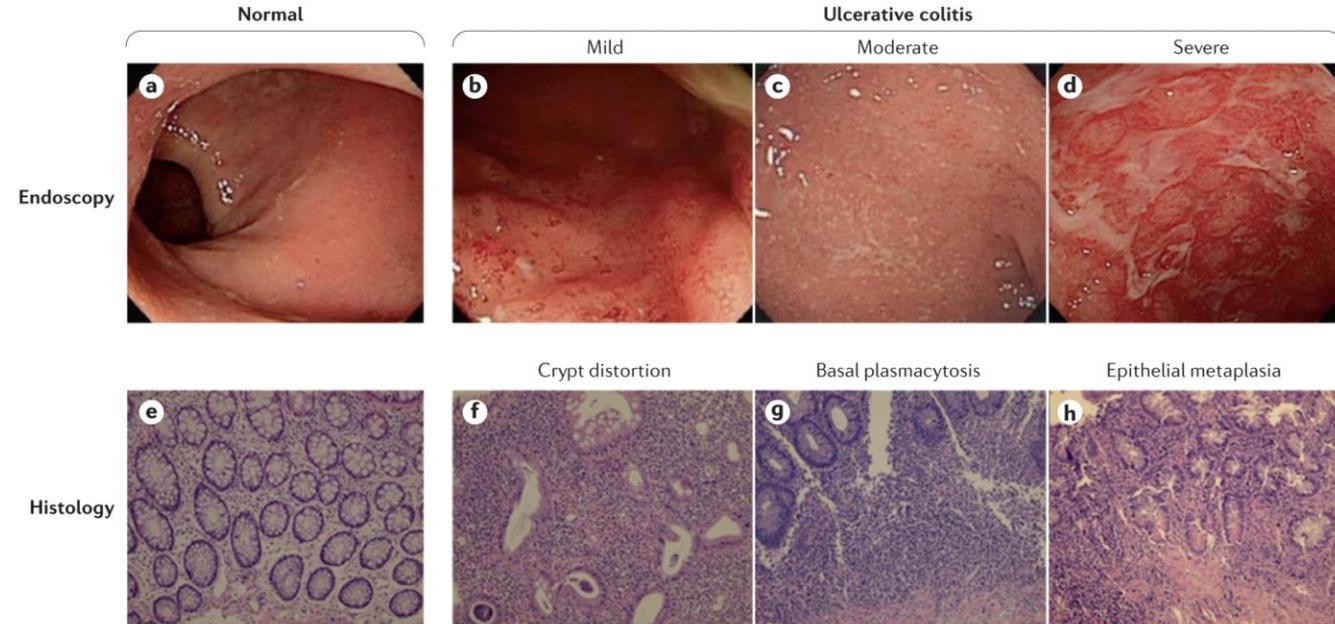
- UC is more common in **developed and Western countries**, but is rising in developing countries
- Globally, an estimated **5 million people** have been diagnosed with UC
- In the United States, an estimated **600,000-900,000** people have UC (0.18 – 0.27% of the population)
- By 2030, India is expected to have the highest burden of IBD by overall numbers



Pathophysiology of ulcerative colitis (UC)



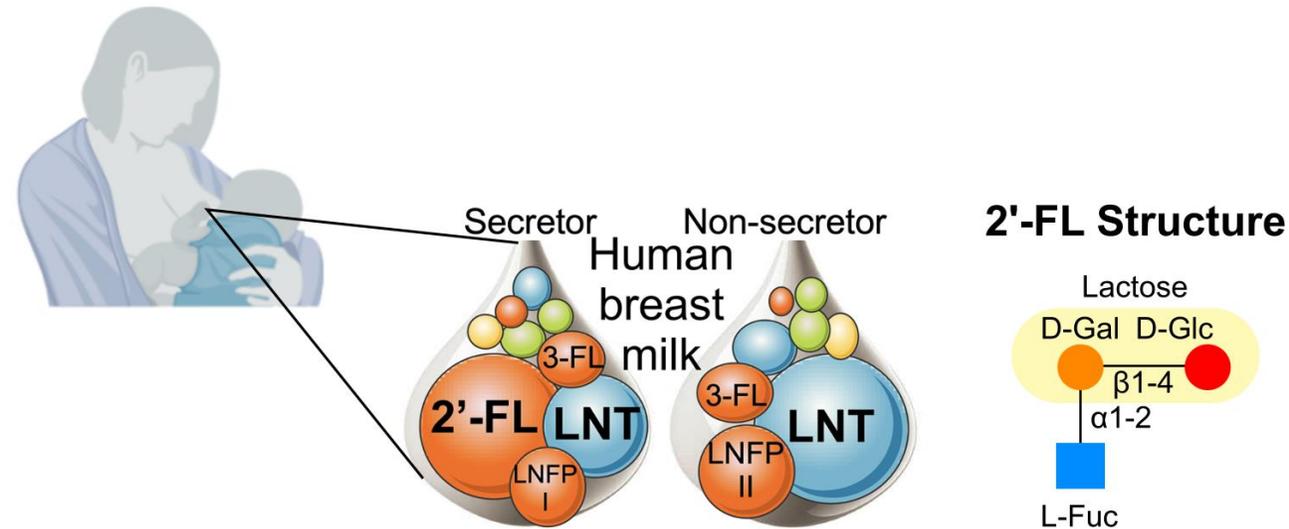
Maintenance of barrier function should be the primary therapeutic aim



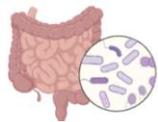
Histopathological features: alterations in mucosal architecture, immune cell infiltration and epithelial abnormality

- **Symptoms:** bloody stool, loose and urgent bowel movements, abdominal cramps and pain, persistent diarrhea, weight loss, loss of appetite, nausea, fever, low energy and fatigue, anemia and delayed growth and development in children
- **Limited treatment options today:** aminosalicylates, corticosteroids (short term), immunomodulators, biologic therapies, Jak inhibitors. **None of these heal the mucosal epithelium.**

Breast milk-derived 2'-fucosyllactose (2'-FL) promotes host health



Positively correlated with child height and weight during the first 5 years of life (Lagström, et al., 2020)



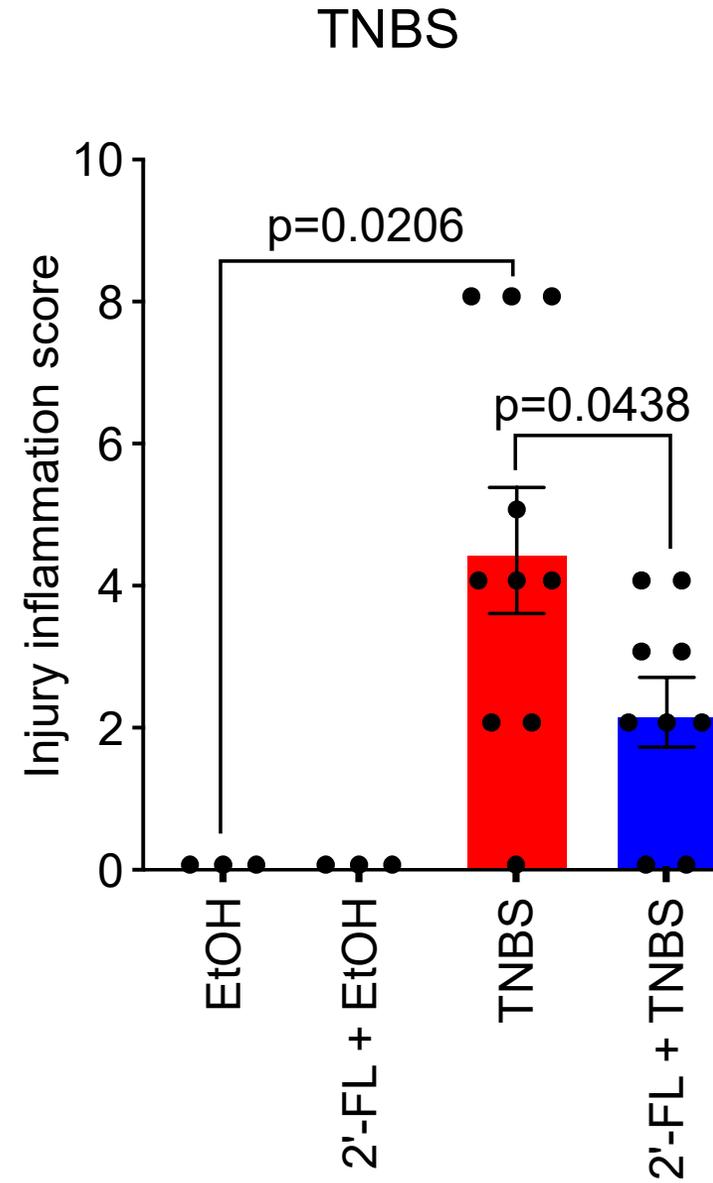
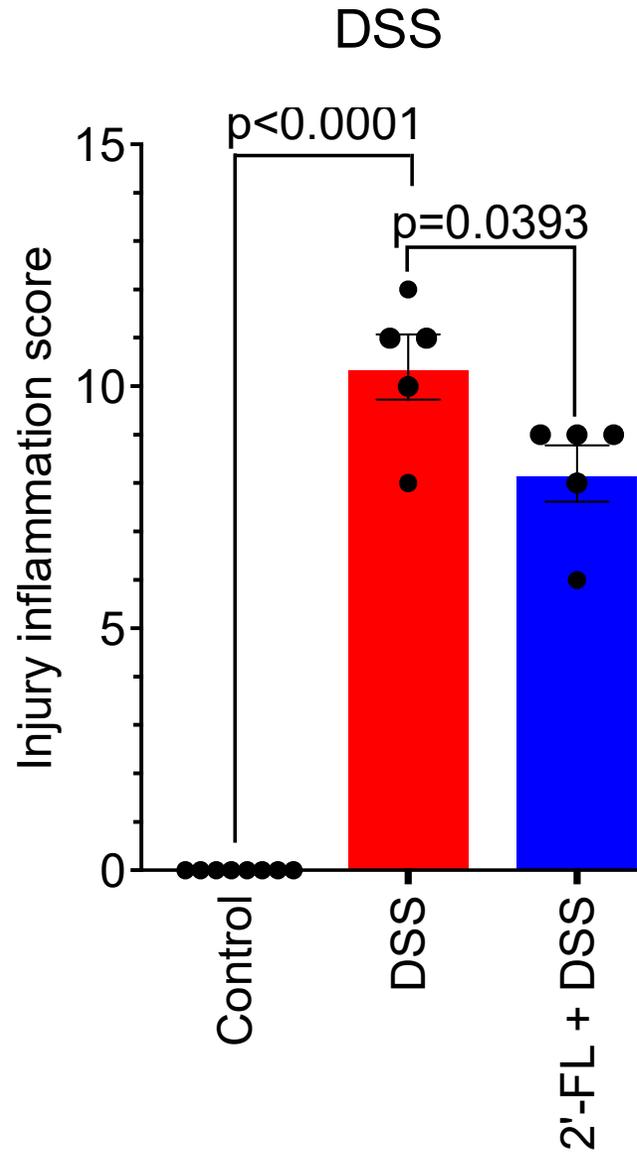
The gut microbial community: \uparrow *Bifidobacterial* colonization and growth (Lewis, et al., 2015)



Intestinal epithelial cells: \uparrow proliferation and differentiation (Kuntz, et al, 2008)
 \downarrow inflammatory responses (Grabinger, et al, 2019)

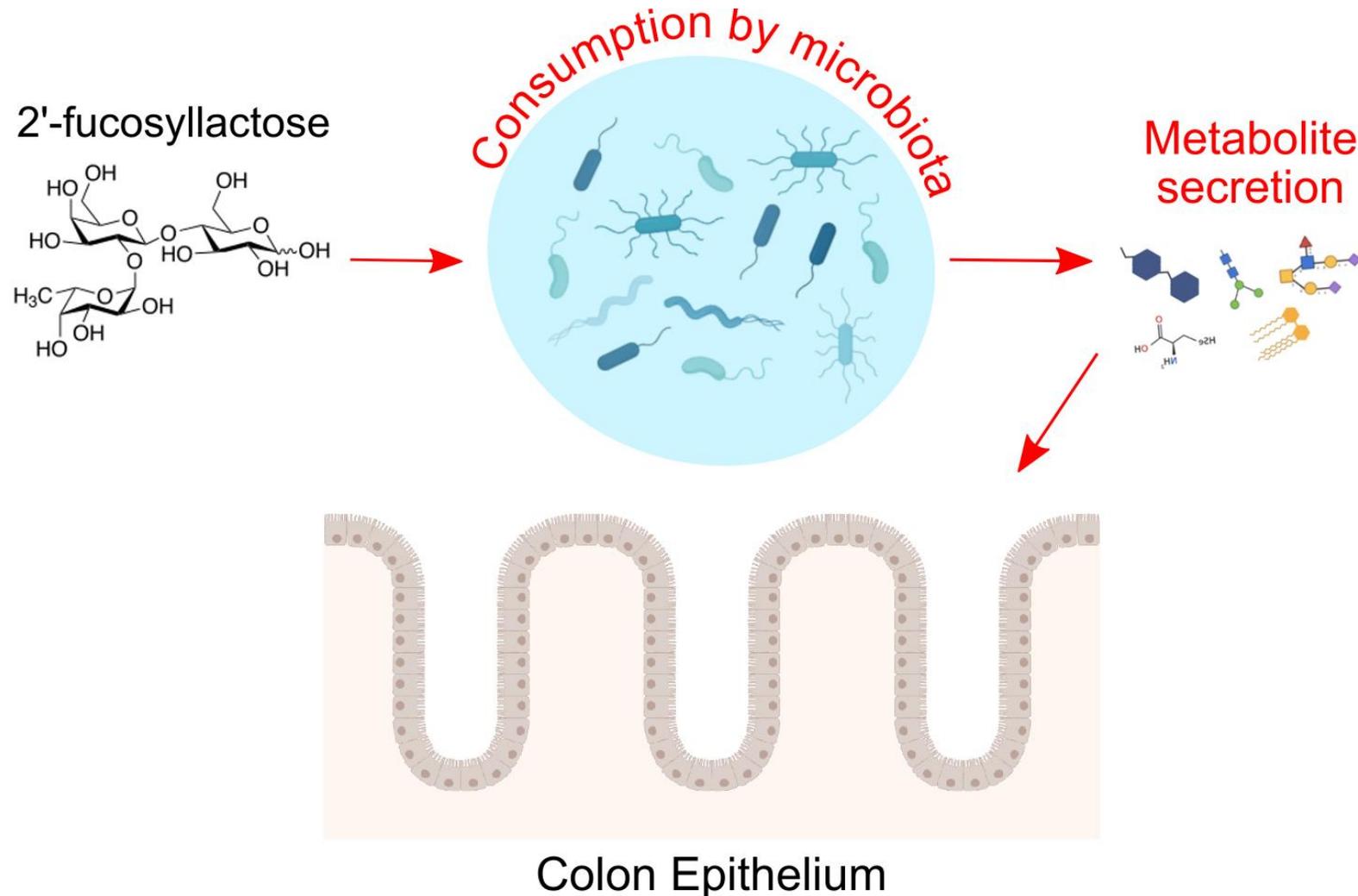
The mechanisms mediating the beneficial effects of 2'-FL on intestinal homeostasis remain largely unknown

2'-FL reduces colonic inflammation and injury in adult mice

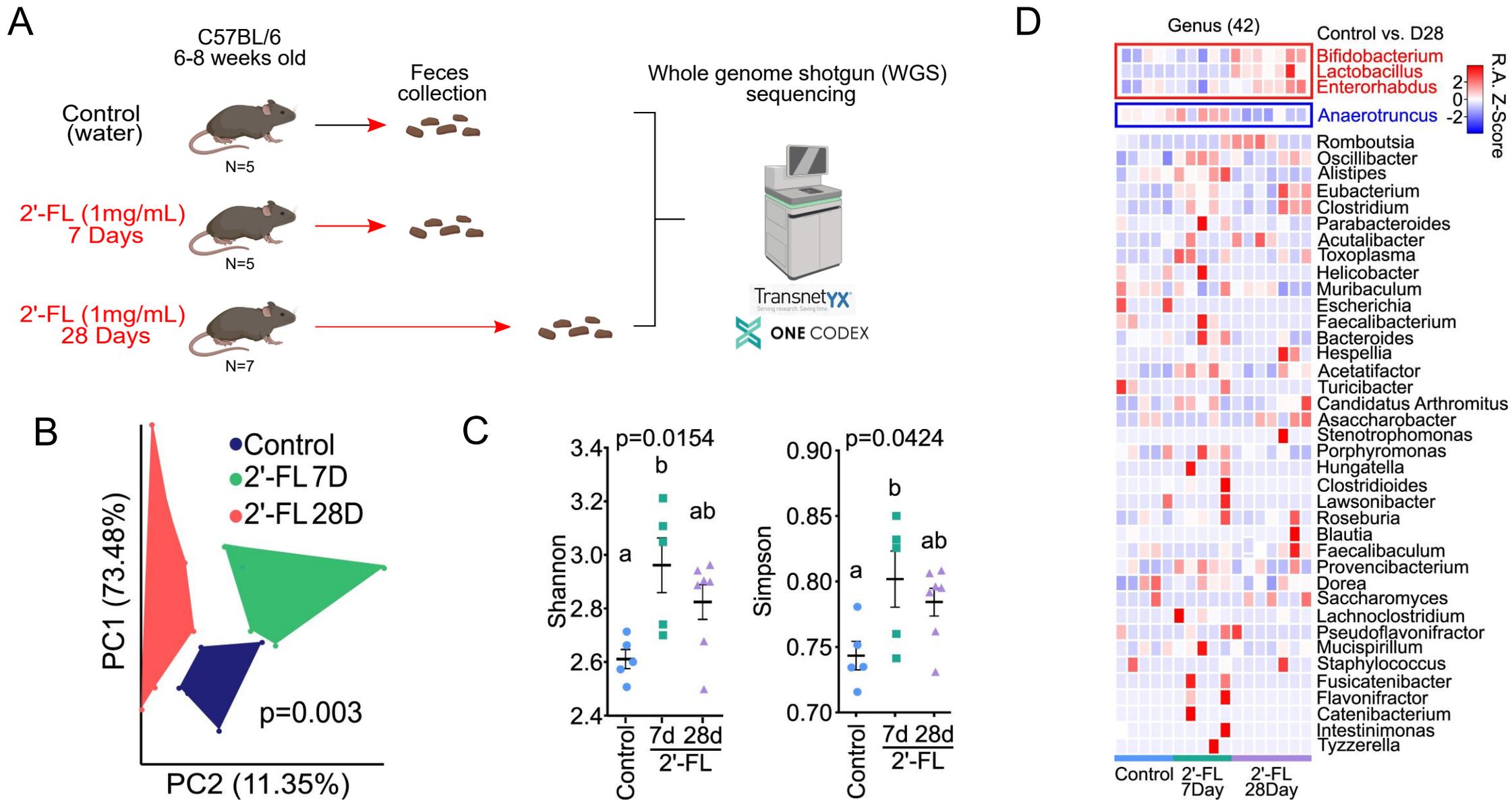


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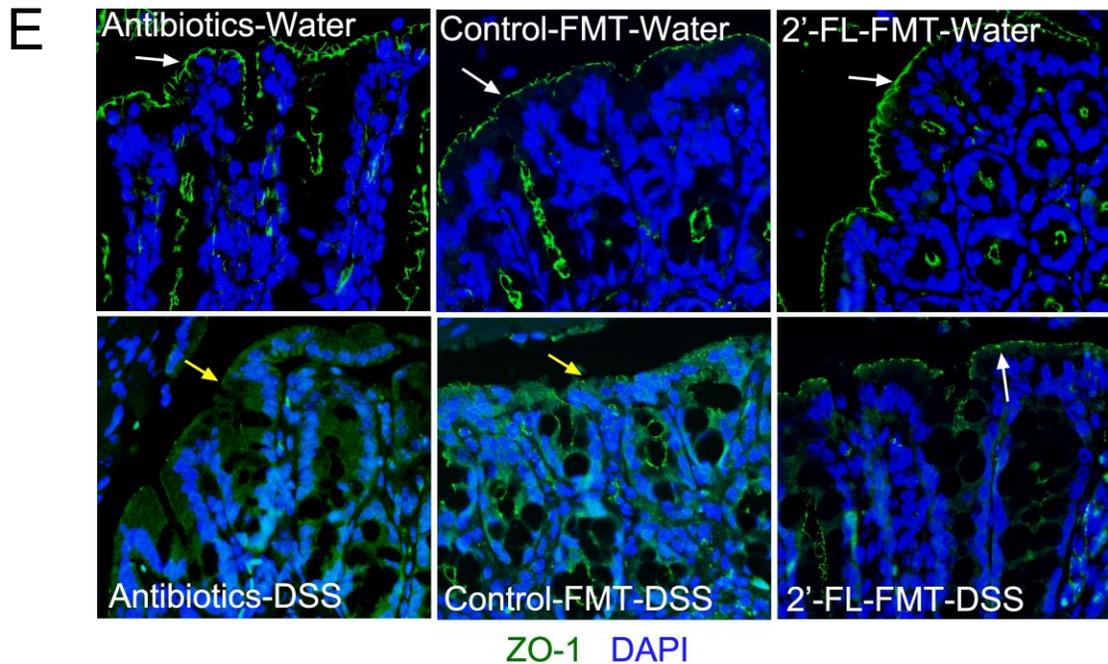
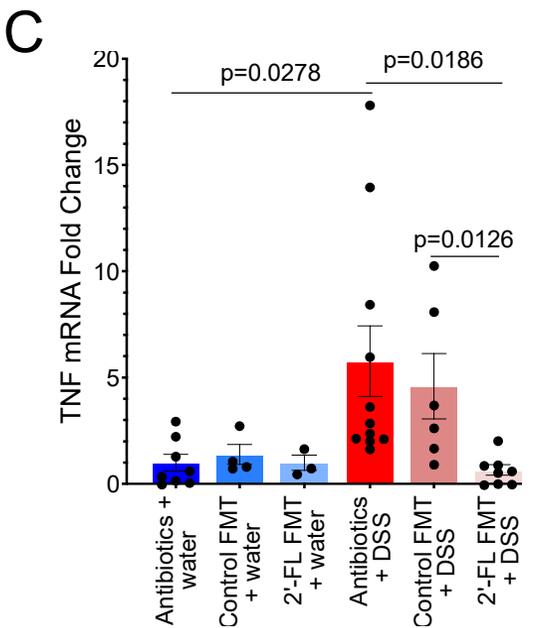
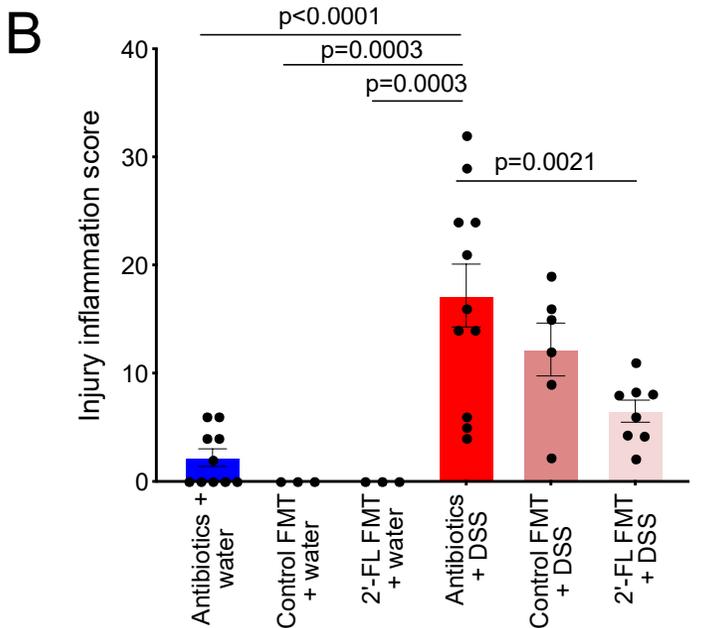
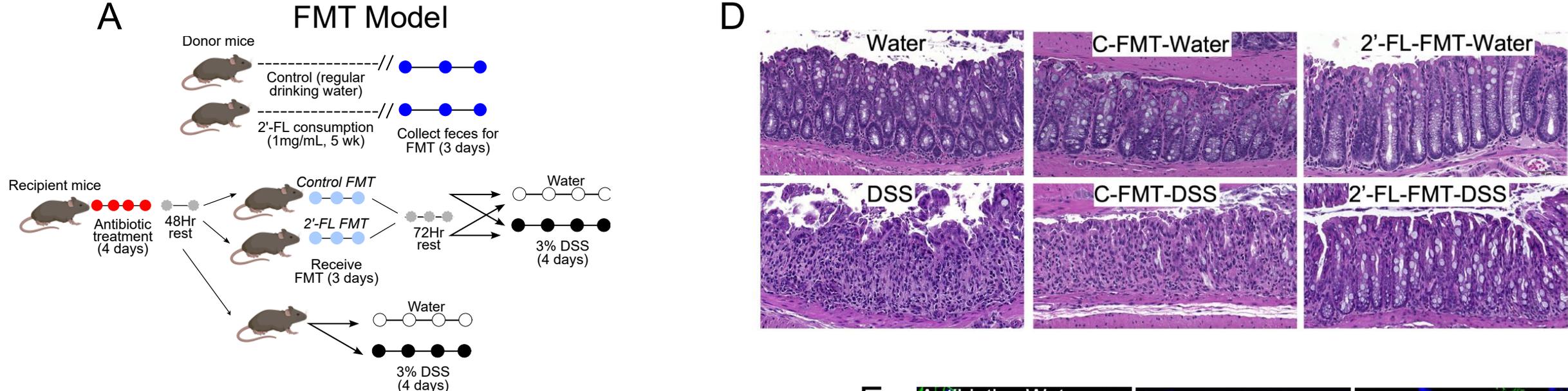
To determine if the effect of 2'-FL on ameliorating intestinal inflammation is mediated through regulation of gut microbial metabolism



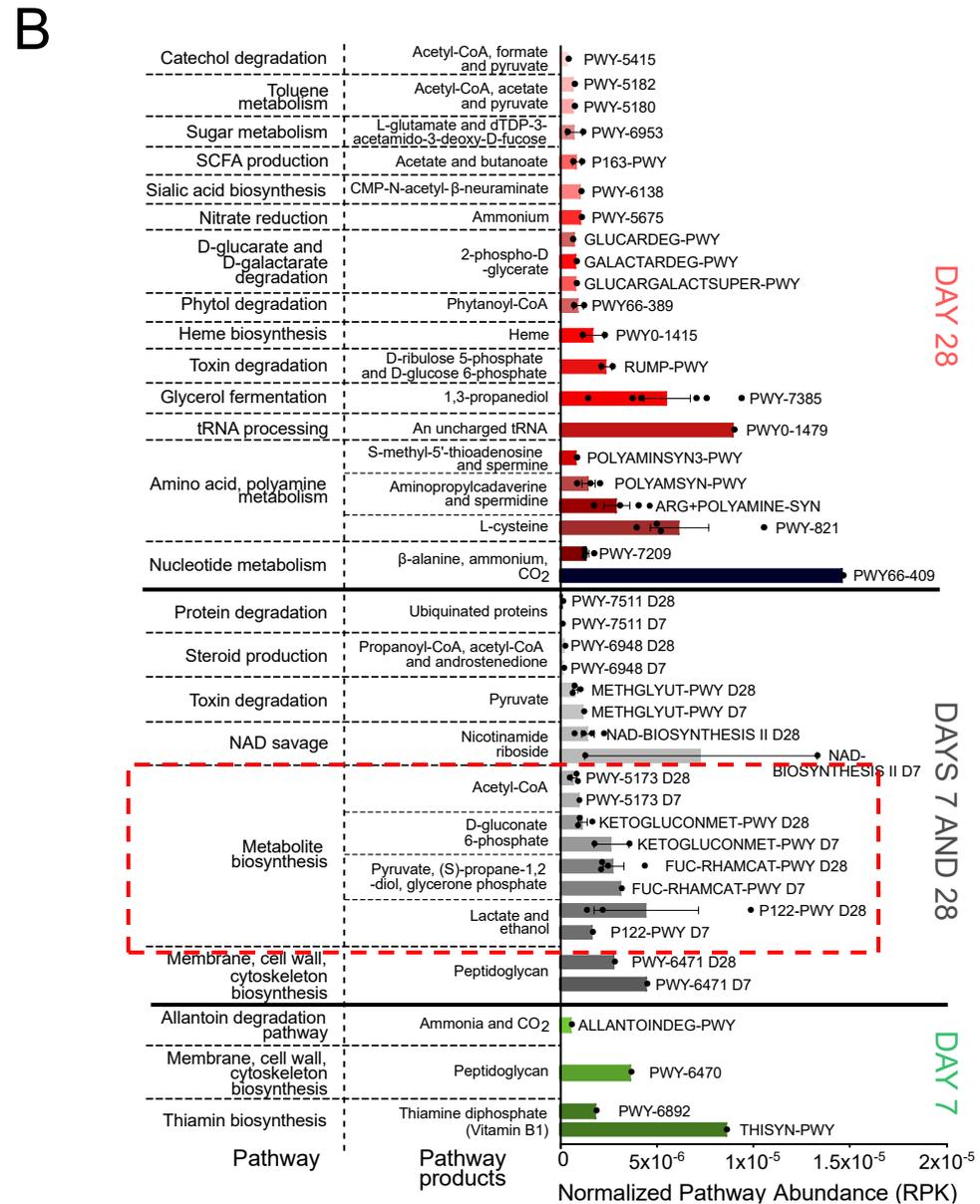
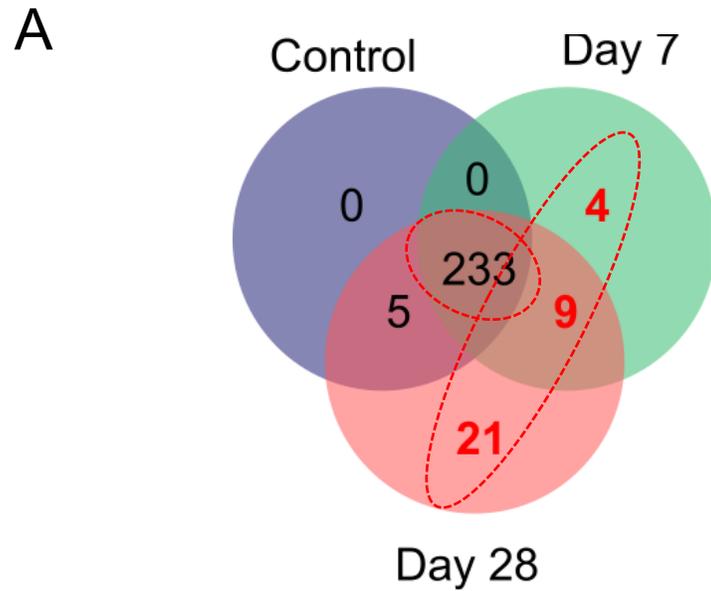
2'-FL modulates the microbiome composition in adult mice



2'-FL-modulated gut microbial community ameliorates DSS-induced injury & colitis in adult mice

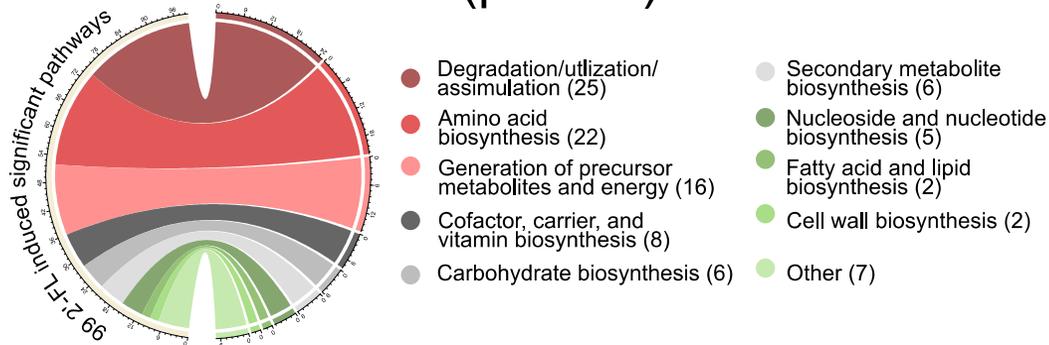


HUMAN 3.0 program analysis: 2'-FL significantly regulates 133 microbial metabolic pathways

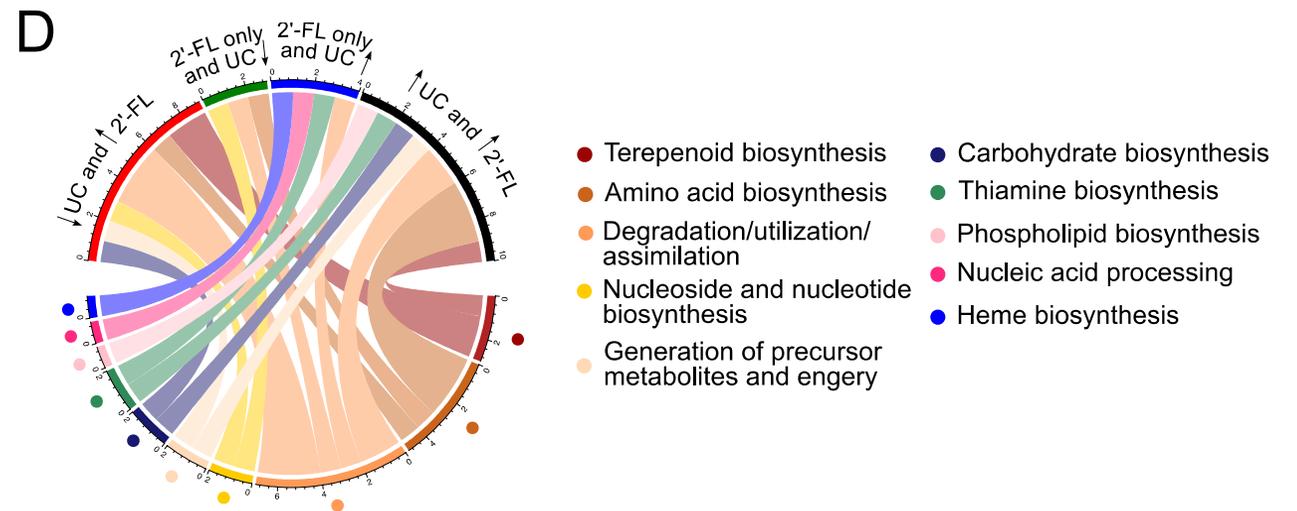
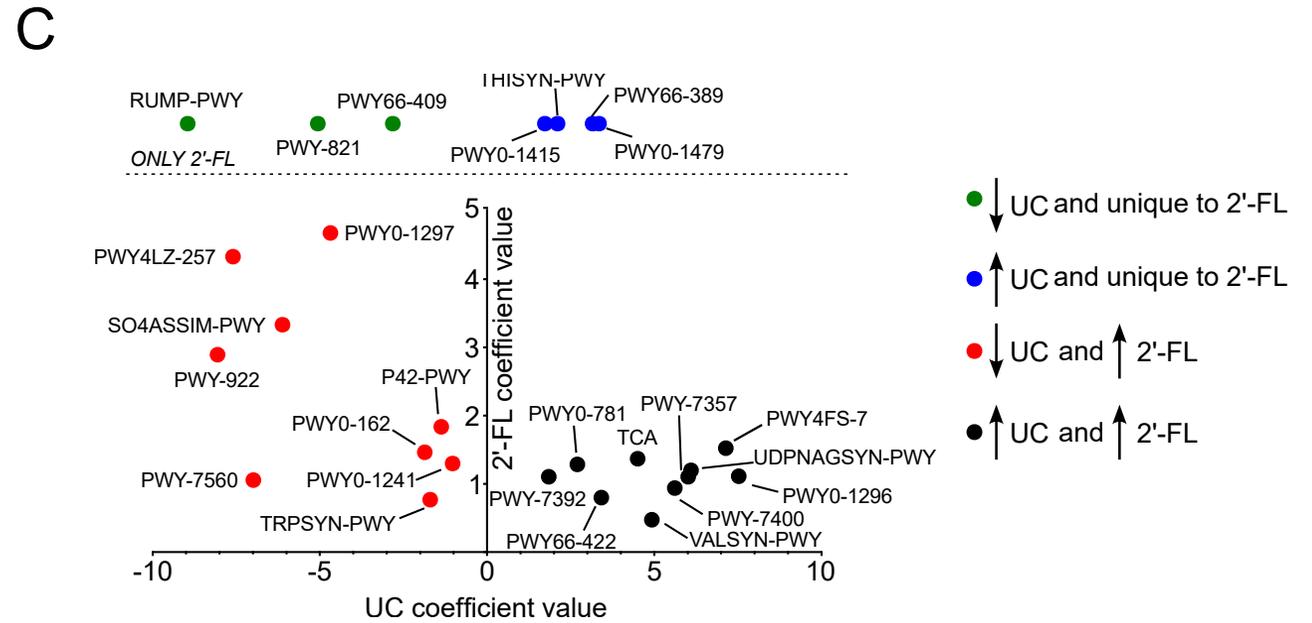
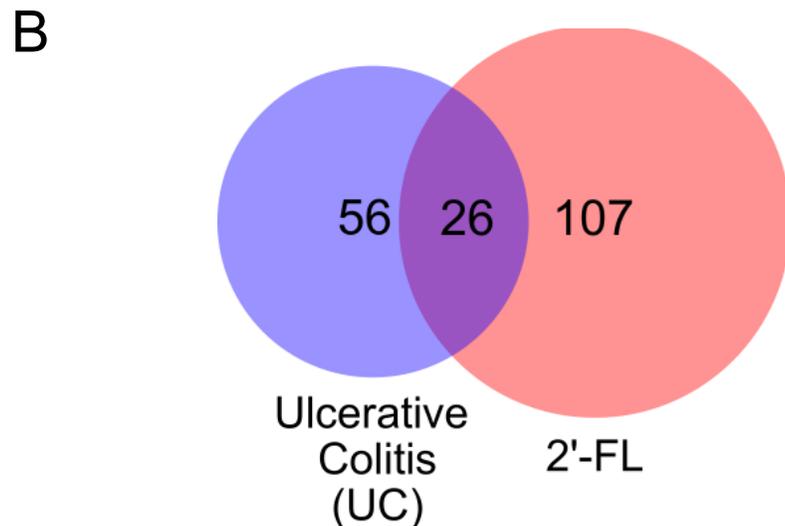
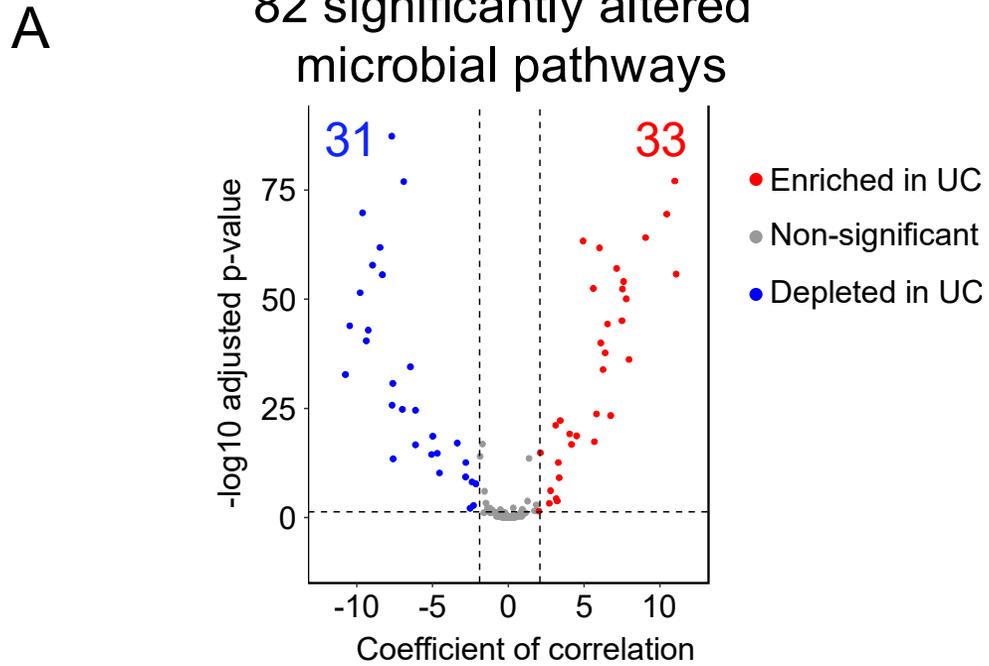


C

2'-FL significantly enriched 99 pathways (p<0.05)



26 microbial metabolic pathways dysregulated in ulcerative colitis are regulated by 2'-FL



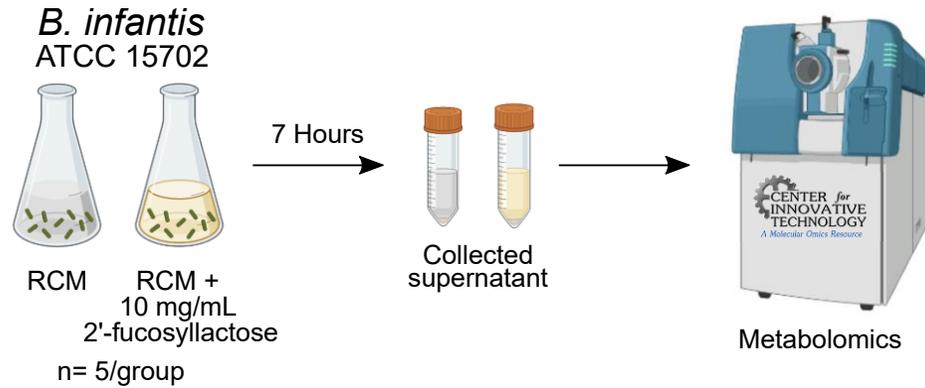
2'-fucosyllactose regulates *Bifidobacterium* function for ulcerative colitis prevention

Bifidobacterium longum subspecies infantis (B. infantis)

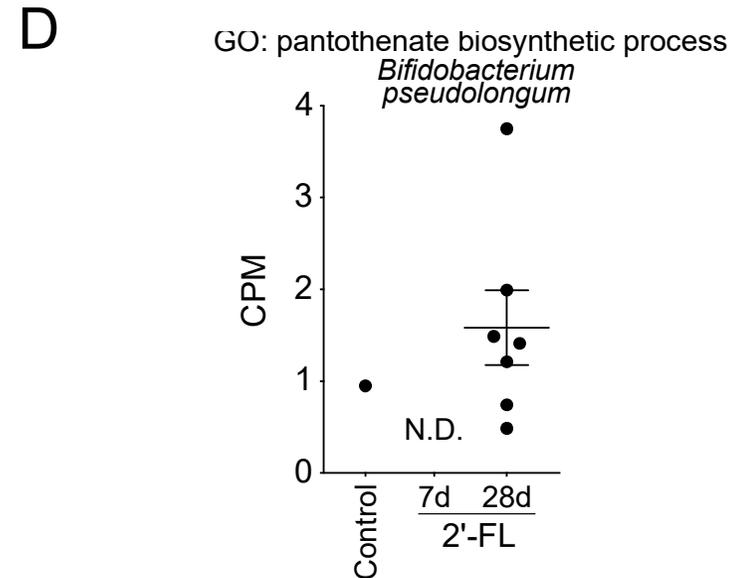
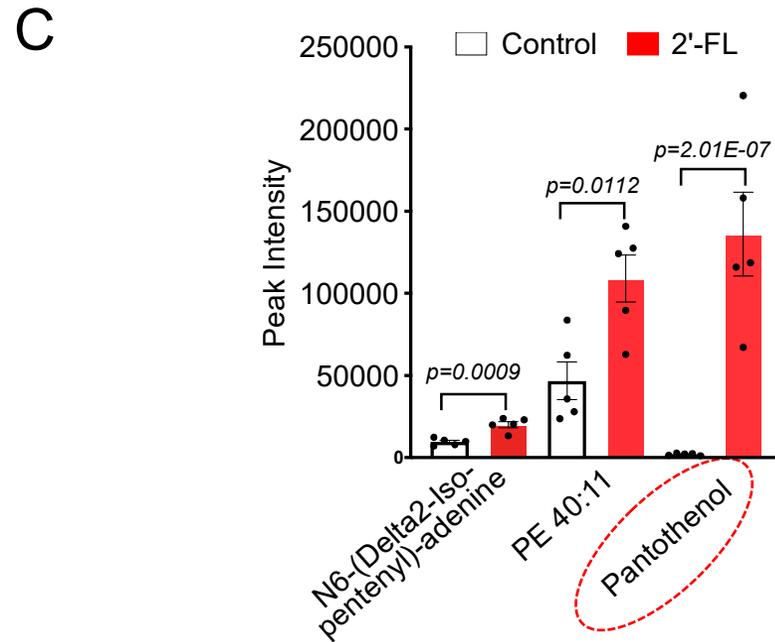
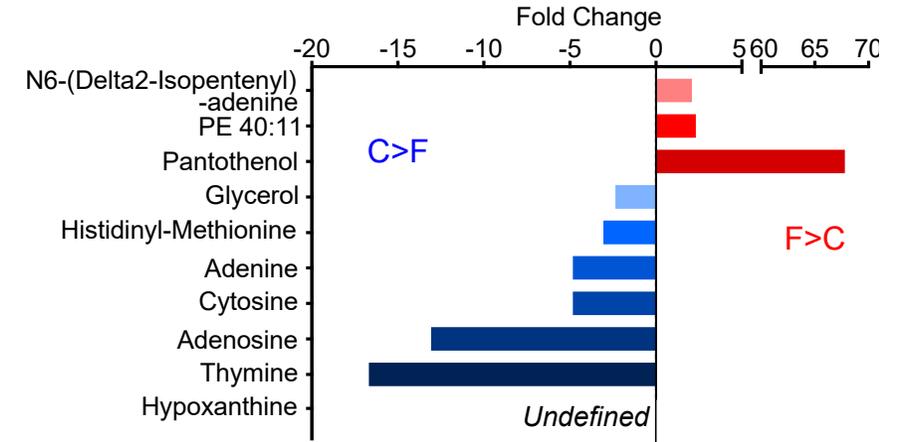
- Enriched in infant versus adult feces (*B. infantis*) and correlated with consumption of human milk oligosaccharides (Yoshioka, et al., 1983; Kleessen, et al., 1995; Favier, et al., 2003)
- Breastfed infants have less GI issues later in life: Meta-analysis of 17 studies found that exclusive breast feeding of any duration was associated with a **reduced risk** of Crohn's disease (odds ratio of 0.67) and ulcerative colitis (odds ratio 0.56) (Klement, et al., 2004)
- Capable of metabolizing/importing HMO's (Sela, et al., 2008)
 - HMO consumption patterns are **strain specific** (Barboza, et al., 2009): *B. longum*, ***B. infantis***, *B. breve*, and *B. bifidum* can consume HMO
- The abundance of *Bifidobacterium* is **strongly reduced in the feces of UC patients** compared to healthy subjects (Duranti, et al., 2016), *Bifidobacterium* is **lower in IBS patients** vs no-IBS controls (Kerckhoffs, et al., 2009; Rajilić-Stojanović, et al., 2011), and patients with **active Chron's disease** have significantly less recoverable bifidobacterial in feces vs healthy individuals (Favier, et al., 1997). Also **reduced in rodent models of colitis** (El-Baz, et al., 2020).

2'-FL stimulates pantothenol secretion by *Bifidobacterium longum* subsp. *infantis*

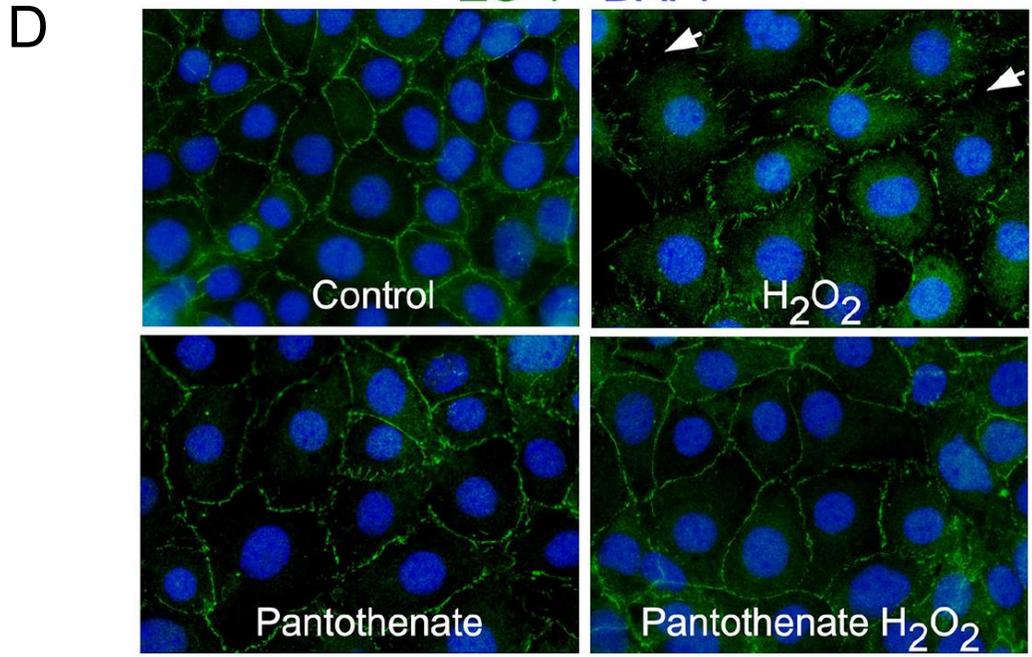
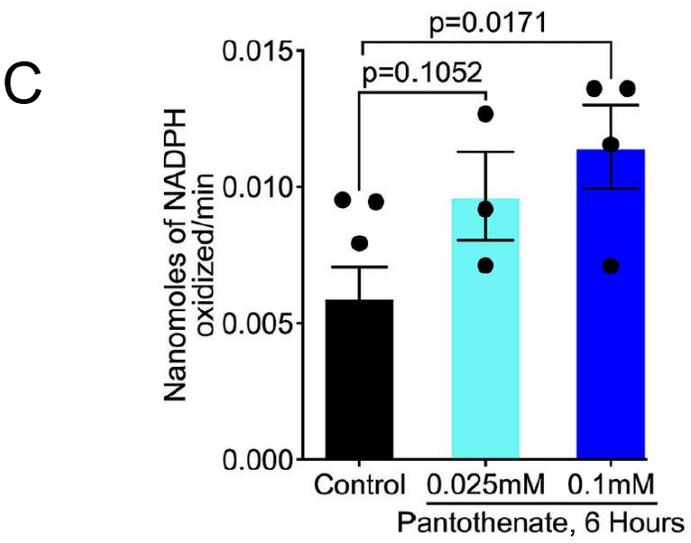
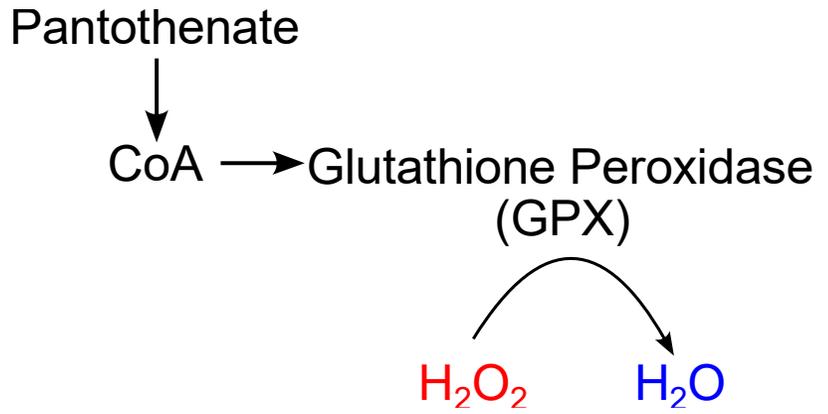
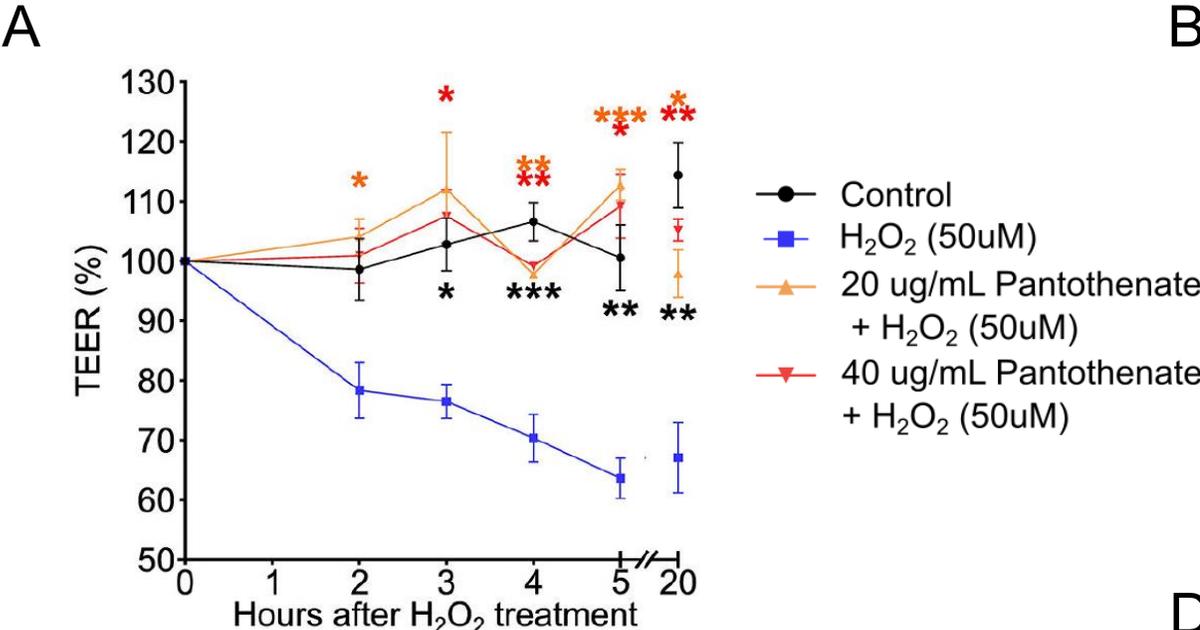
A Untargeted metabolomics



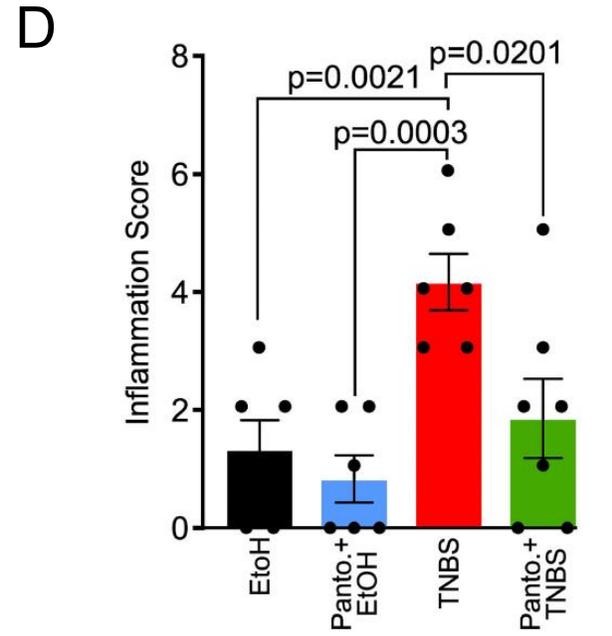
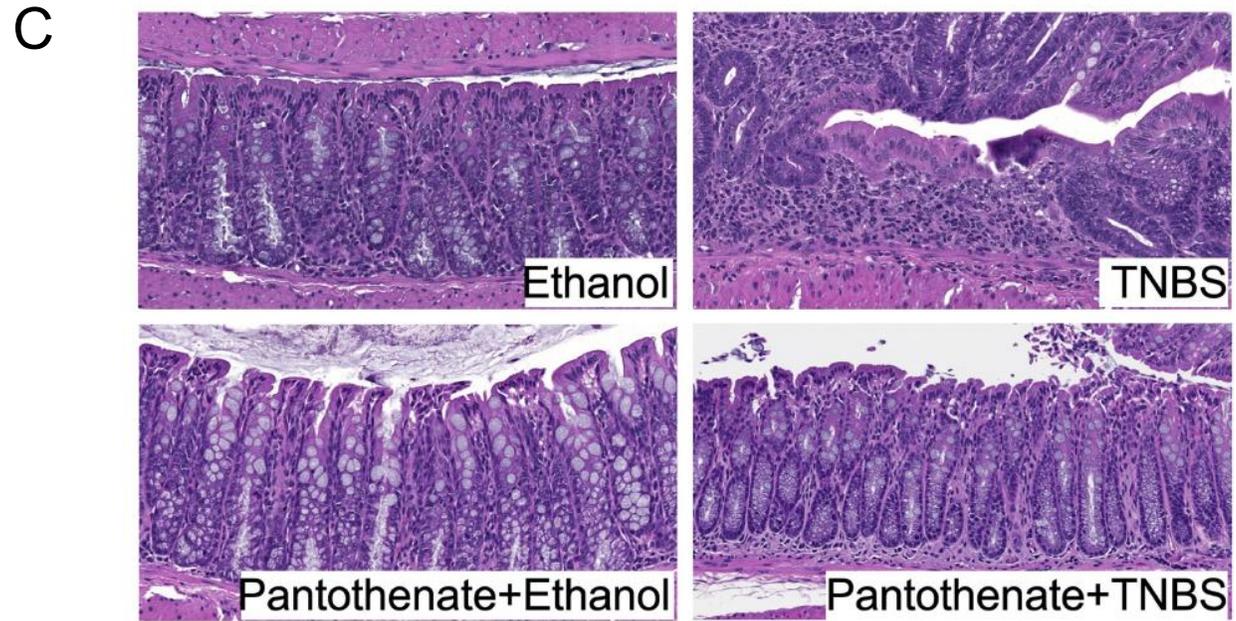
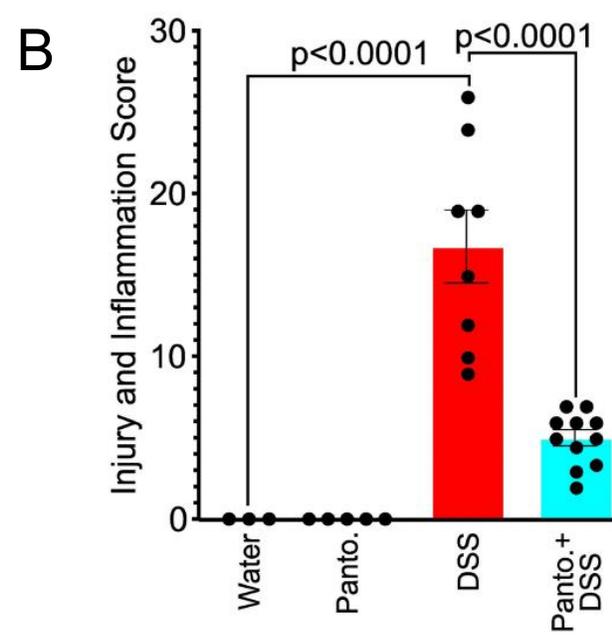
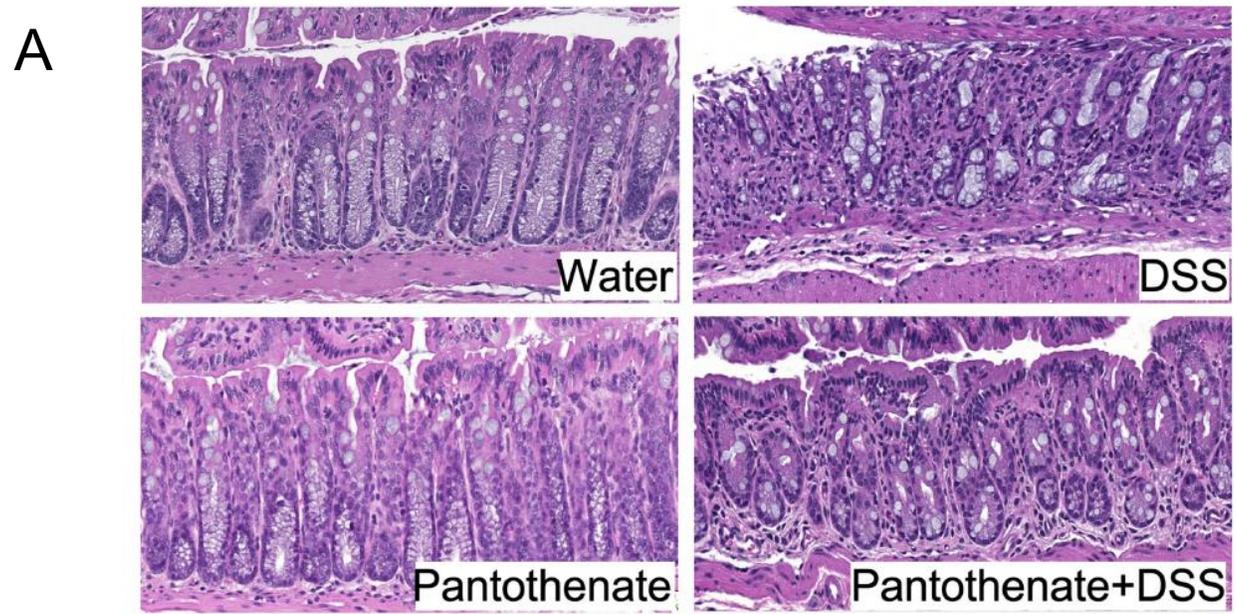
B Levels 1, 2 and 3 Metabolites ($p < 0.05$)



Pantothenate (Vitamin B5) preserves the epithelial barrier and mitigates oxidative stress

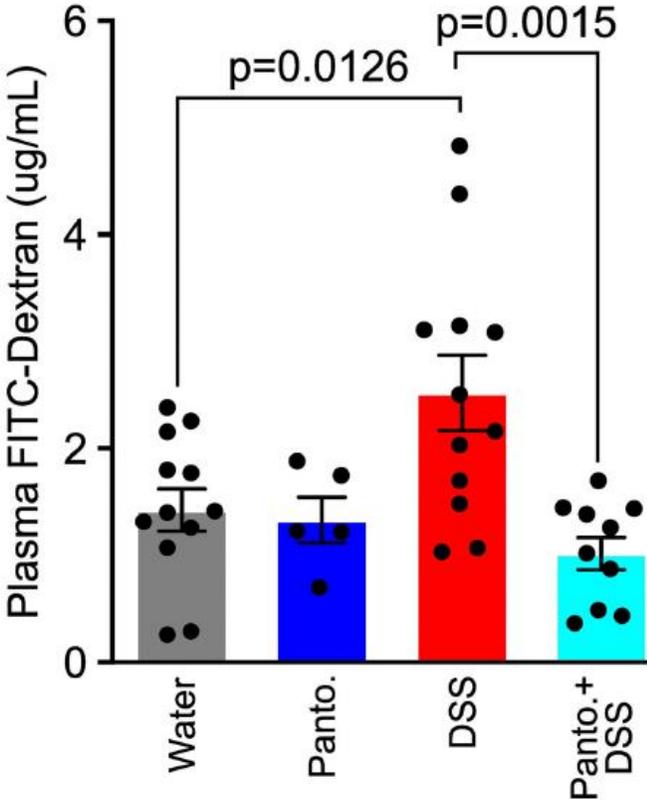


Pantothenate prevents epithelial barrier disruption and reduces inflammation *in vivo*

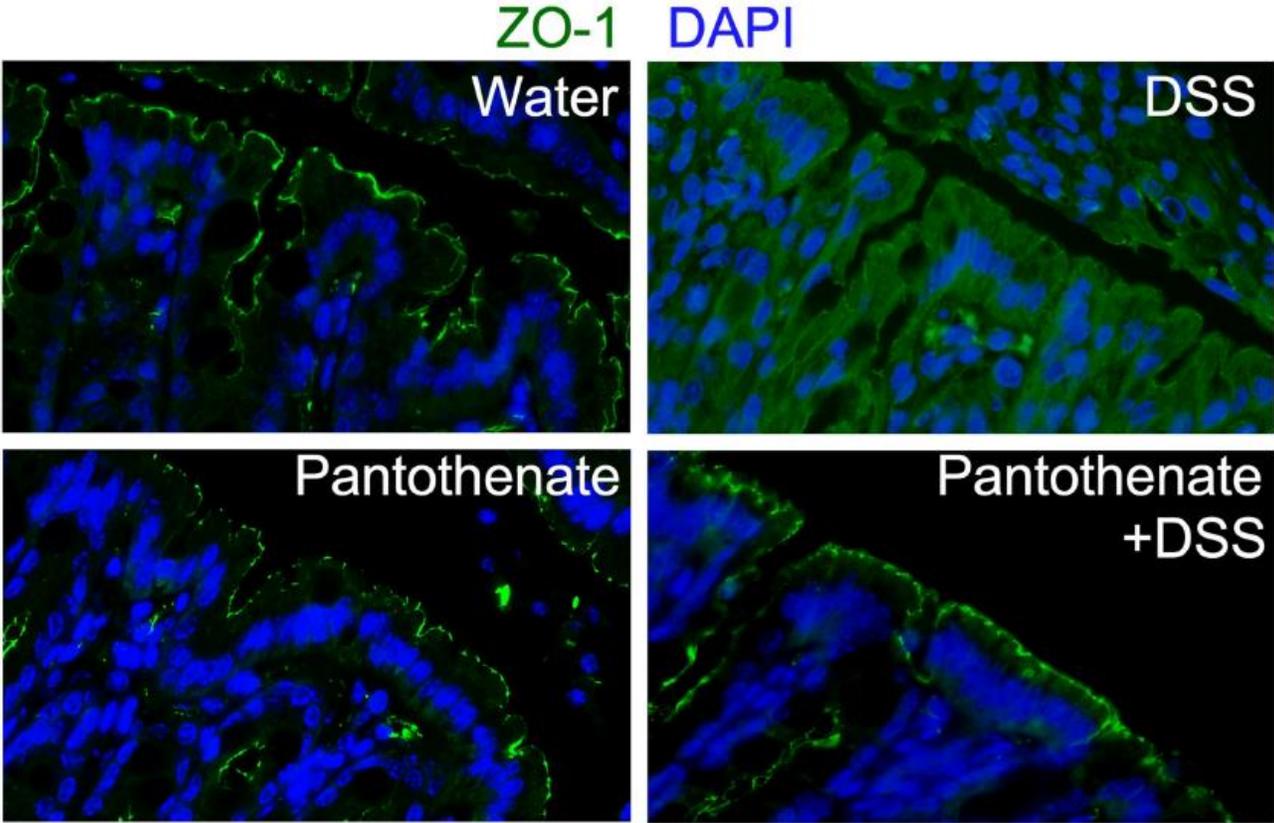


Pantothenate prevents epithelial barrier disruption and reduces inflammation *in vivo*

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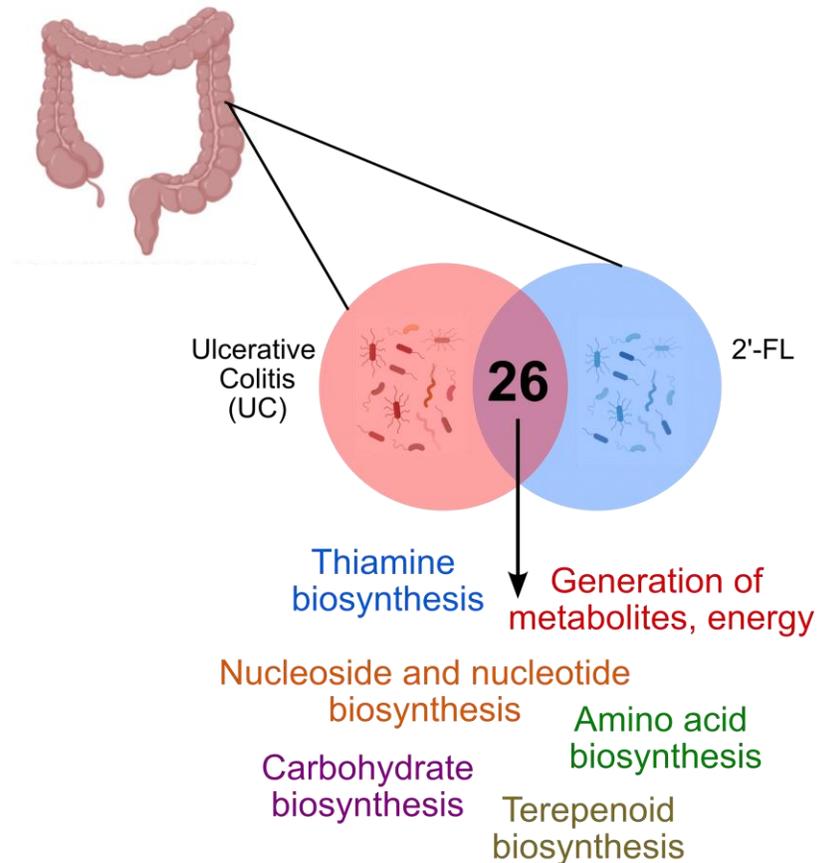


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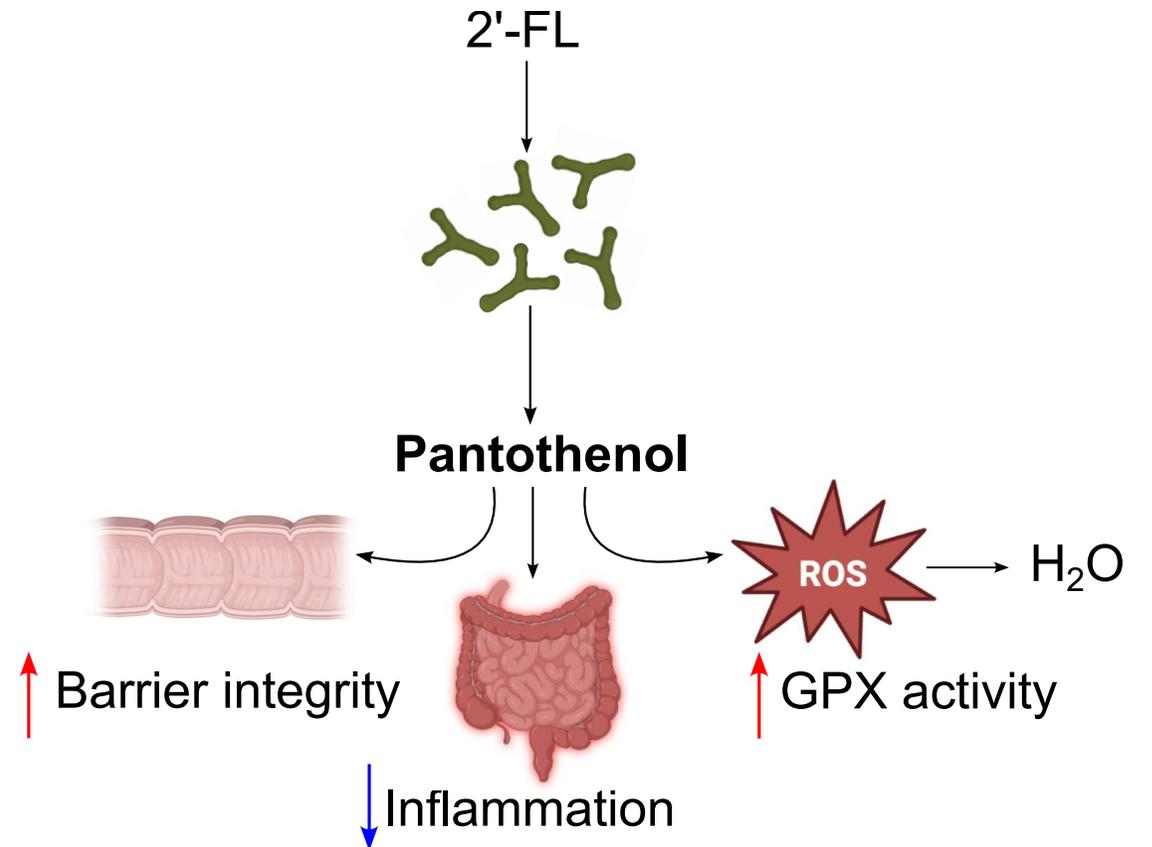


2'-FL prevents colitis through regulation of gut microbial metabolism

26 significantly altered microbial metabolic pathways in IBD are regulated by 2'-FL



Bifidobacterium infantis catabolizes 2'-FL into pantothenol to protect intestinal integrity and prevent colitis



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