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Inflammatory cytokines and microbial ligands and metabolites interact to modulate DUOX2 expression and activity

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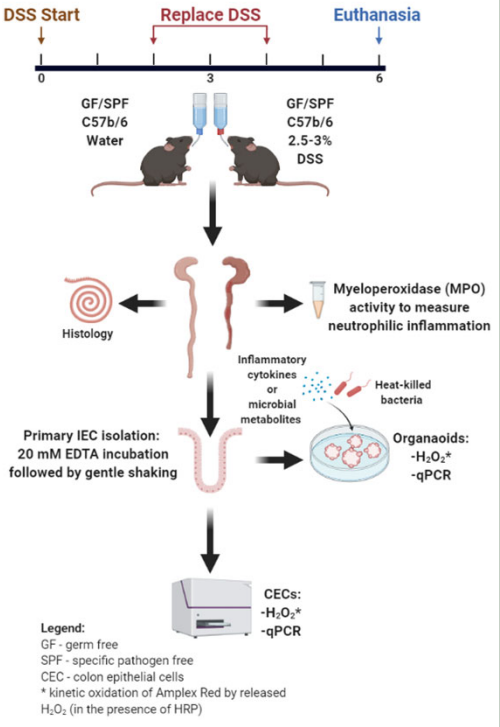
Background

- The pathogenesis of inflammatory bowel diseases (IBD) is characterized by a dysregulated crosstalk between the host and the microbiome that leads to the development of inflammation and dysbiosis.
- Dysbiosis in IBD involves an expansion of Proteobacteria and a reduction of Firmicutes, particularly of butyrate-producing species such as Faecalibacterium prausnitzii.
- The epithelial NADPH oxidase dual oxidase 2 (DUOX2), which prevents bacterial colonization of the mucosa through the production of hydrogen peroxide (H_2O_2), is the only gene consistently altered in IBD patients before the onset of disease.
- However, the involvement of DUOX2 in IBD is not well understood. We aimed to define how inflammation and the microbiota regulate DUOX2 activity.

Hypothesis

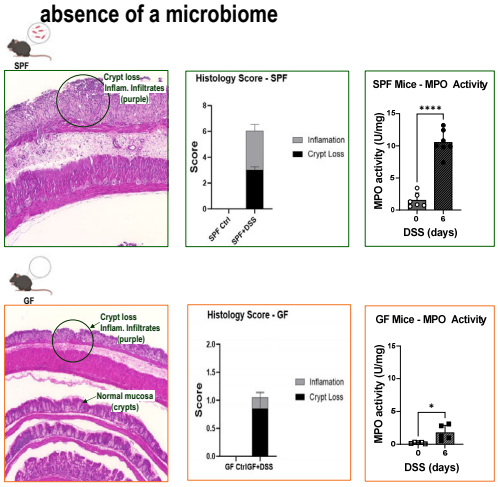
- We hypothesized that the increase in epithelial DUOX2 activity is a response to both inflammatory and microbial signals.

Methods

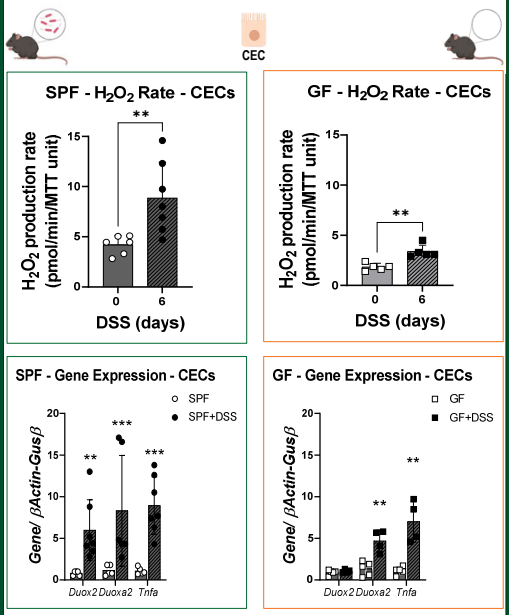


Results I

- **Chemical colitis induces inflammation in the absence of a microbiome**

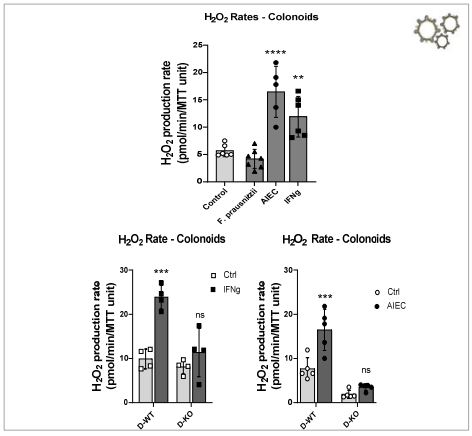


- **DUOX2 responds to inflammation in the absence of a microbiome**

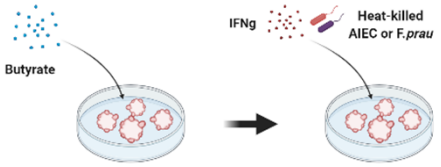


Results II

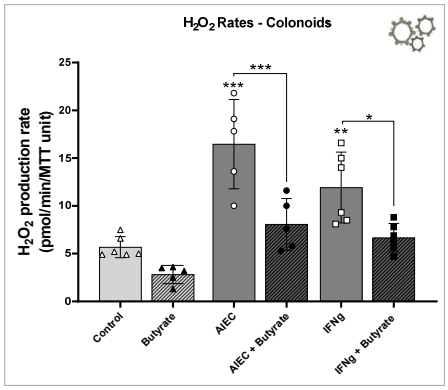
- **DUOX2 responds to pathobionts and inflammation in vitro**



- **Butyrate inhibits epithelial ROS production in vitro**



Legend:
AIEC - adherent invasive Escherichia coli strain LF82
F.prau - F. prausnitzii strain A2-165



Conclusions

- Inflammation and AIEC induce the expression and activity of DUOX2.
- The microbial metabolite butyrate abrogates DUOX2 mediated release of H_2O_2.
- Restitution with butyrate-producing species may be beneficial in IBD.

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