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# Role of *Dact3* in the intestinal homeostasis: Elucidating the mechanisms of Action of the anti-inflammatory Commensal bacterium *Faecalibacterium duncaniae* A2-165

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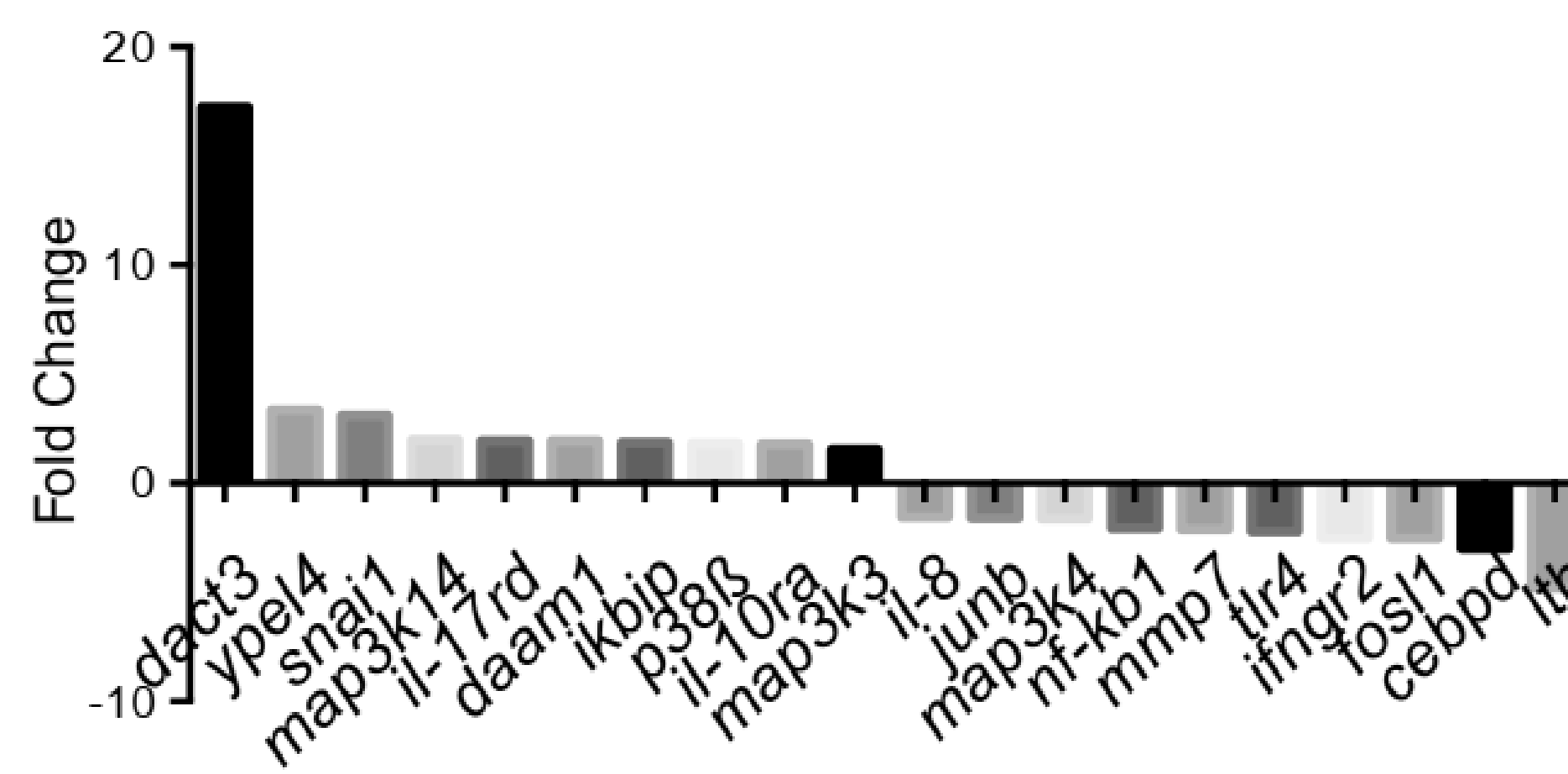
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## INTRODUCTION AND RESEARCH HYPOTHESIS

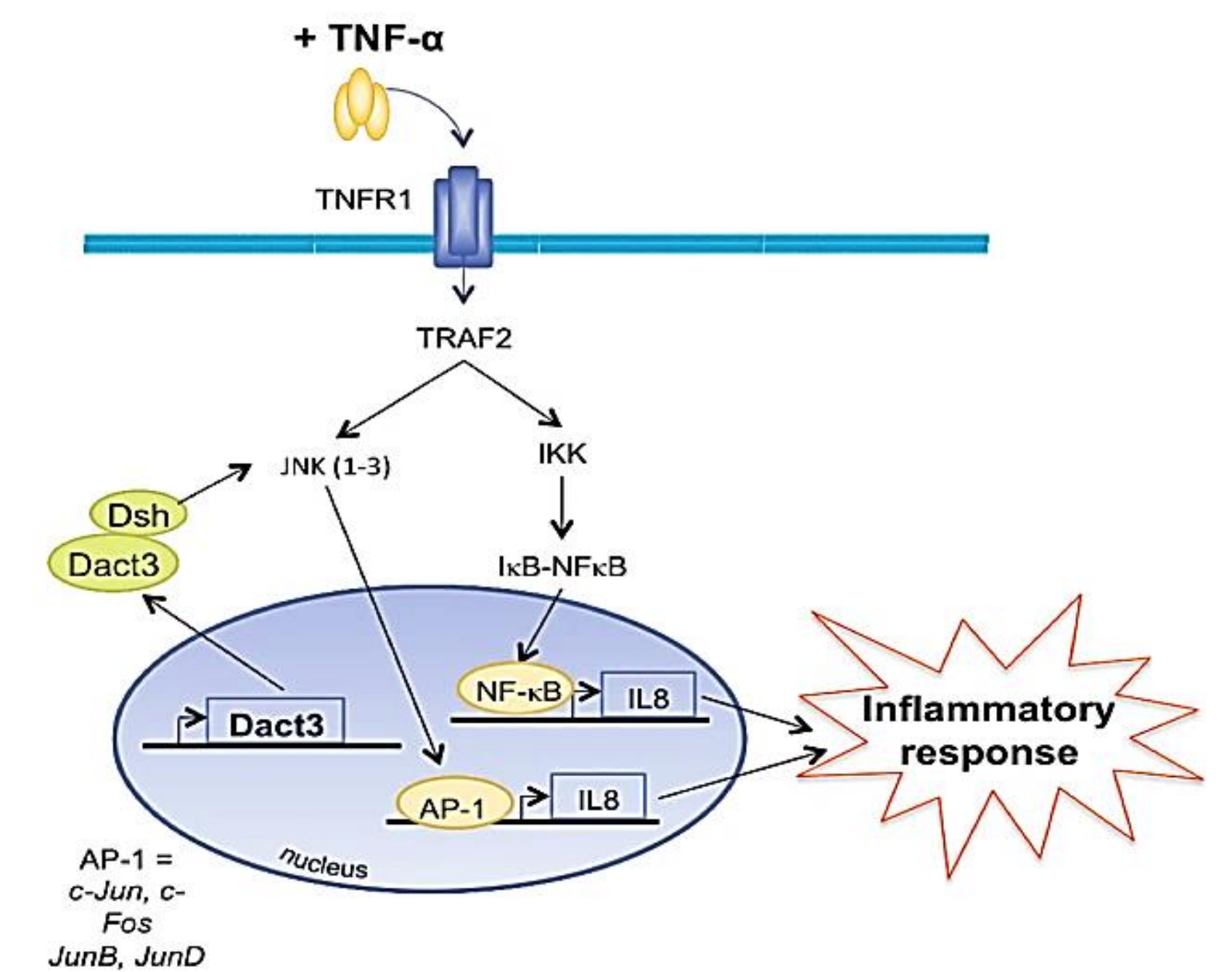
Inflammatory bowel diseases (IBD) are chronic inflammatory disorders of the gut with a substantial socioeconomic and health impact worldwide. A potential approach to prevent and treat IBD is the oral administration of probiotic and commensal bacteria. Interestingly, the commensal bacterial strain *Faecalibacterium duncaniae* A2-165 (former species *Faecalibacterium prausnitzii*) plays a key role in IBD and represents a biomarker of general health. However, the host molecular mechanisms responsible for these anti-inflammatory effects remain poorly studied.

In order to determine the impact of *F. duncaniae* on intestinal epithelial cells (IECs) such as HT-29 (tumoral cells), we performed a transcriptomic approach on these cells, stimulated with TNF- $\alpha$  and exposed to *F. duncaniae* culture supernatant (SN). We found that several genes involved in inflammatory signaling pathways were affected by TNF- $\alpha$  stimulation and *F. duncaniae* SN treatment. In particular, we observed a strong upregulation of *Dact3*, a gene linked to the Wnt/JNK pathway, which is part of the inflammatory process. Strikingly, silencing of *Dact3* expression results in a partial loss of the anti-inflammatory effects (IL-8 inhibition) of *F. duncaniae* SN, suggesting an important role of *Dact3* in these effects. Interestingly, butyrate was identified as one of the *F. duncaniae* effector responsible for *Dact3* modulation and IL-8 inhibition.

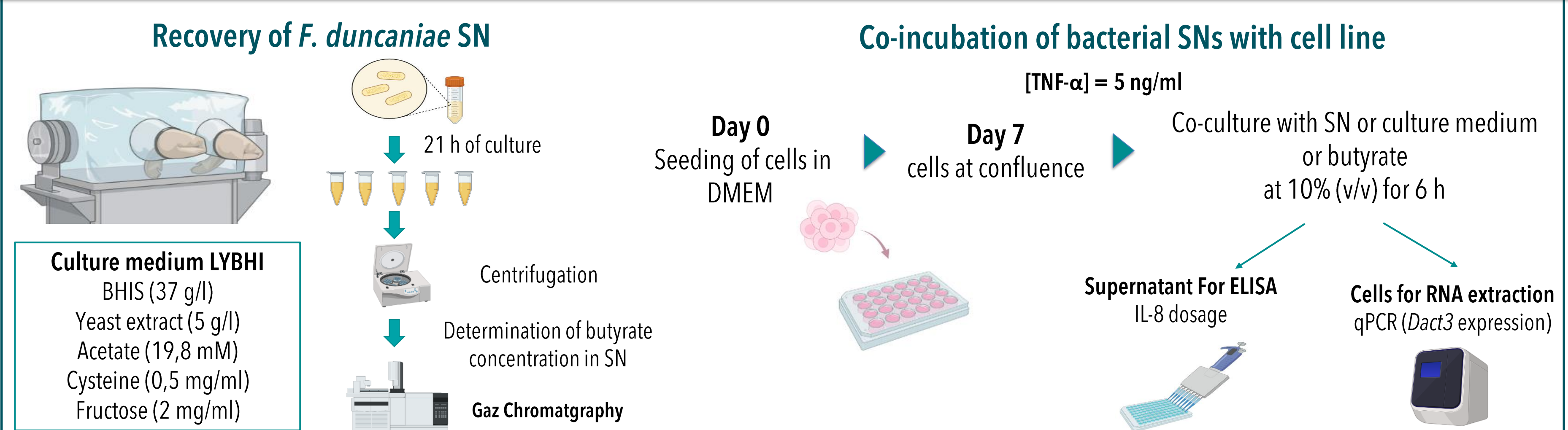
These exciting results provide new clues about the host molecular mechanisms involved in the anti-inflammatory effects of *F. duncaniae*.



Transcriptomic analysis of TNF- $\alpha$ -stimulated HT-29 cells and exposed to *F. duncaniae* SN.



## MATERIAL AND METHODS

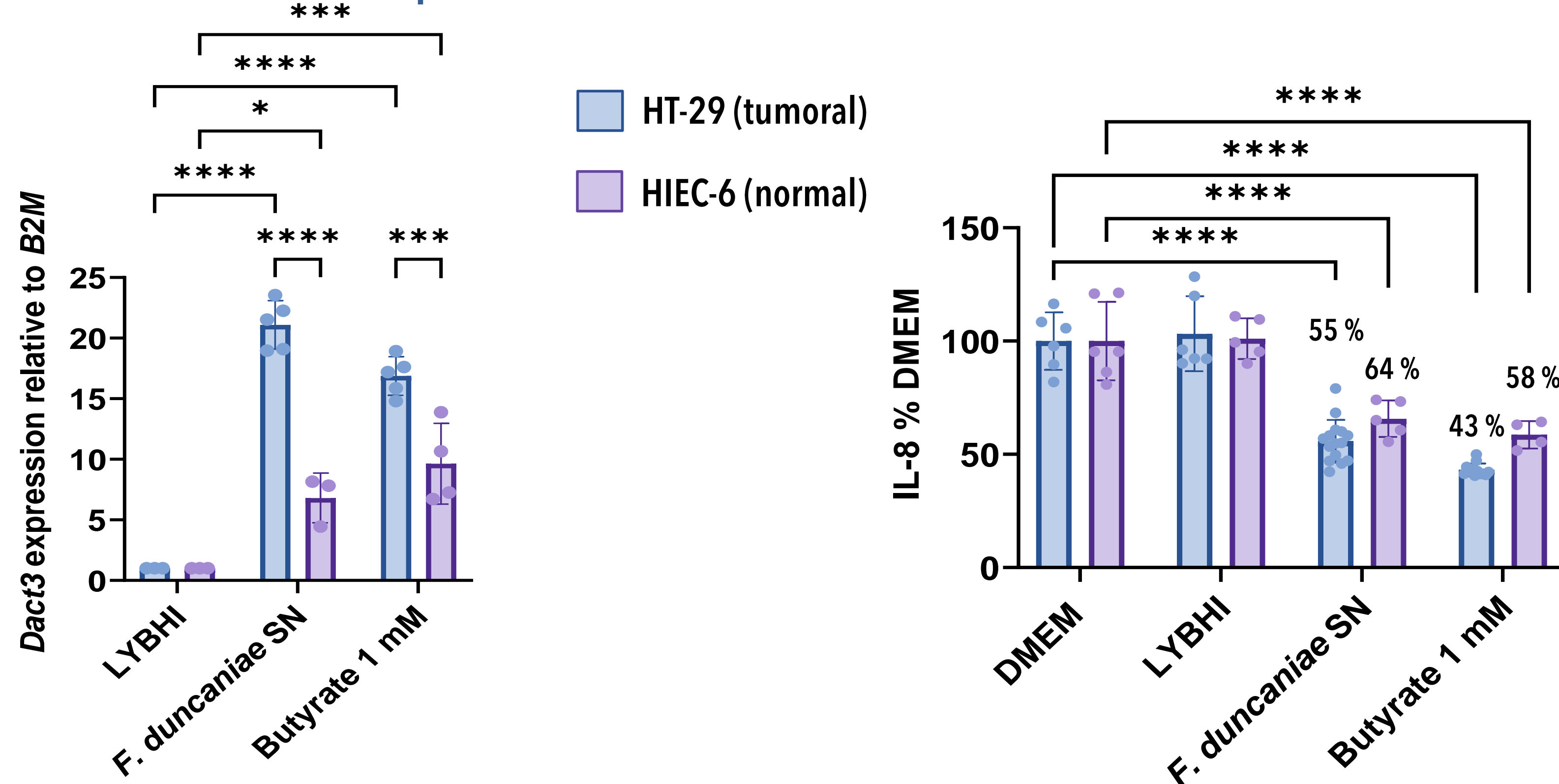


## OBJECTIVES

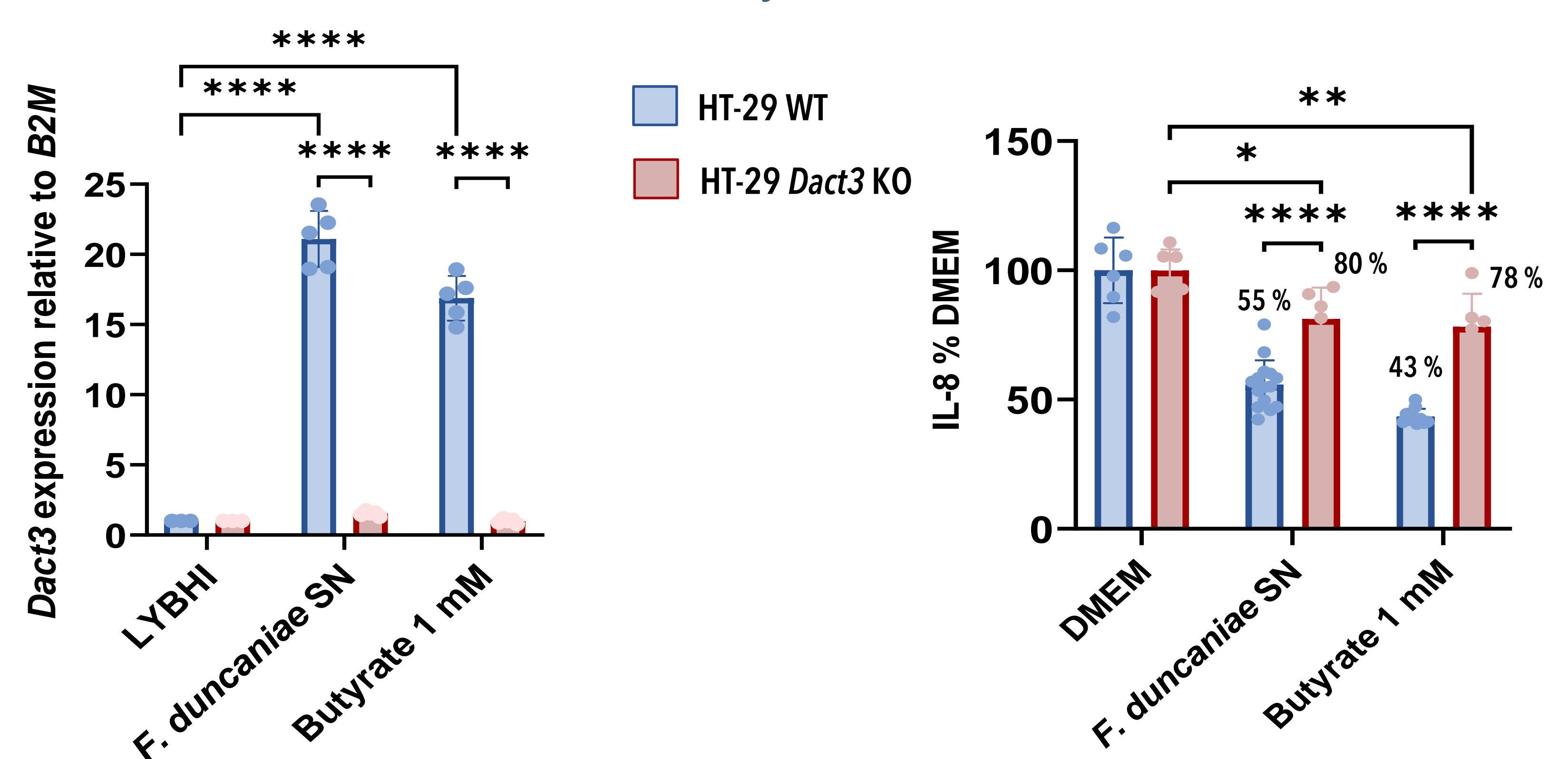
The aim of this study is to determine the role of *Dact3* in intestinal homeostasis and to elucidate the impact of *F. duncaniae* and gut microbiota on *Dact3* expression

## RESULTS

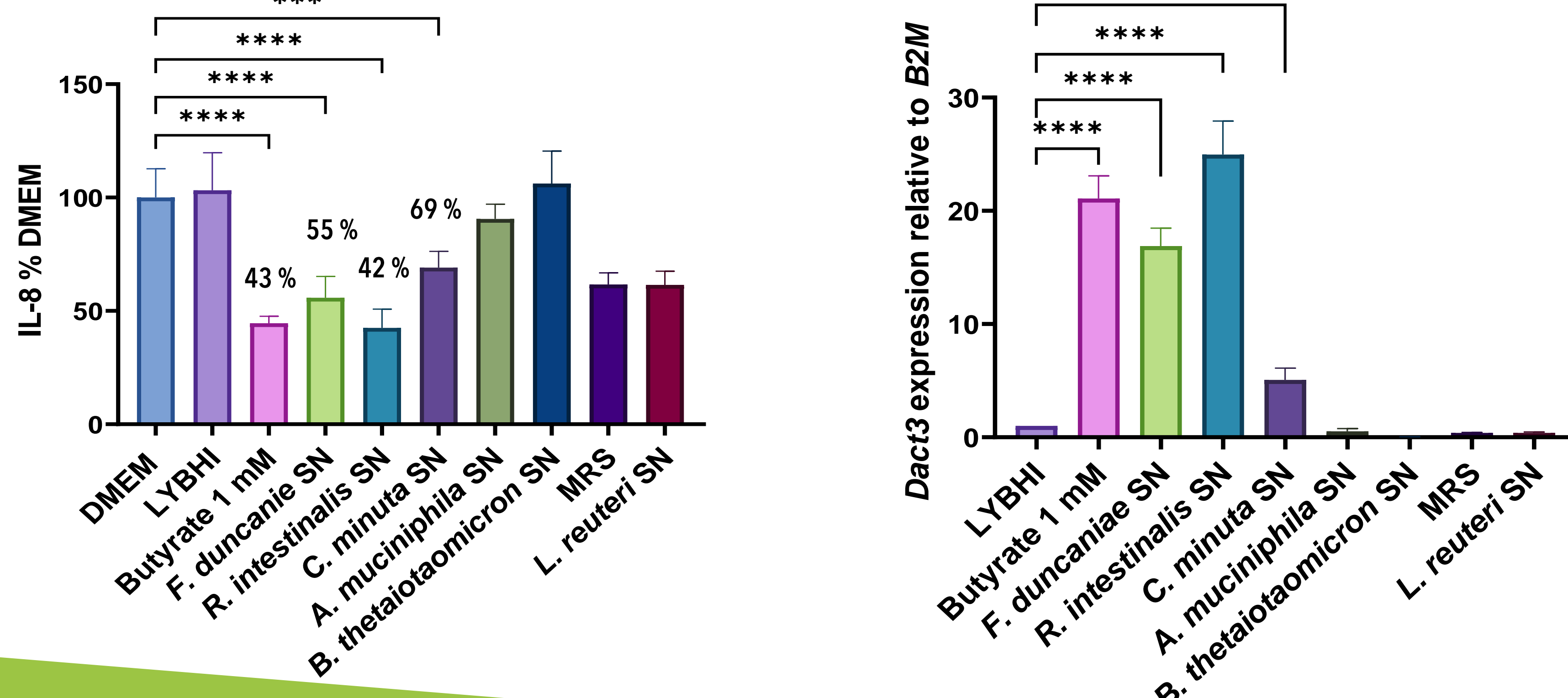
### *F. duncaniae* SN leads to an upregulation of *dact3* and is able to reduce IL-8 production in both TNF- $\alpha$ stimulated cell lines



### *Dact3* knockout by CRISPR/Cas9 in HT-29 cells results in a significant loss of the anti-inflammatory effects of *F. duncaniae* SN



### Confirmation that butyrate is one of *F. duncaniae* effectors responsible of *dact3* modulation and IL-8 inhibition



### Butyrate concentration in SNs

Sample	[butyrate]
LYBHI	0,168 mM
MRS	0,0961 mM
<i>F. duncaniae</i> A2-165 SN	14,85 mM
<i>R. intestinalis</i> SN	16,018 mM
<i>A. muciniphila</i> SN	0,116 mM
<i>B. thetaiotaomicron</i> SN	0,0865 mM
<i>L. reuteri</i> (grown in MRS) SN	0,116 mM
<i>C. Minuta</i> SN	3,12 mM

SNs are diluted 10X in co-culture

## PERSPECTIVES

- Evaluation of *Dact3* overexpression in HT-29 cell line
- Evaluation of *F. duncaniae* SN on *Dact3* expression in murine intestinal organoids
- Determination of the intermediary host receptor responsible for butyrate - *Dact3* interaction
- In vivo* models: determination of the susceptibility of *Dact3* KO mice to colitis