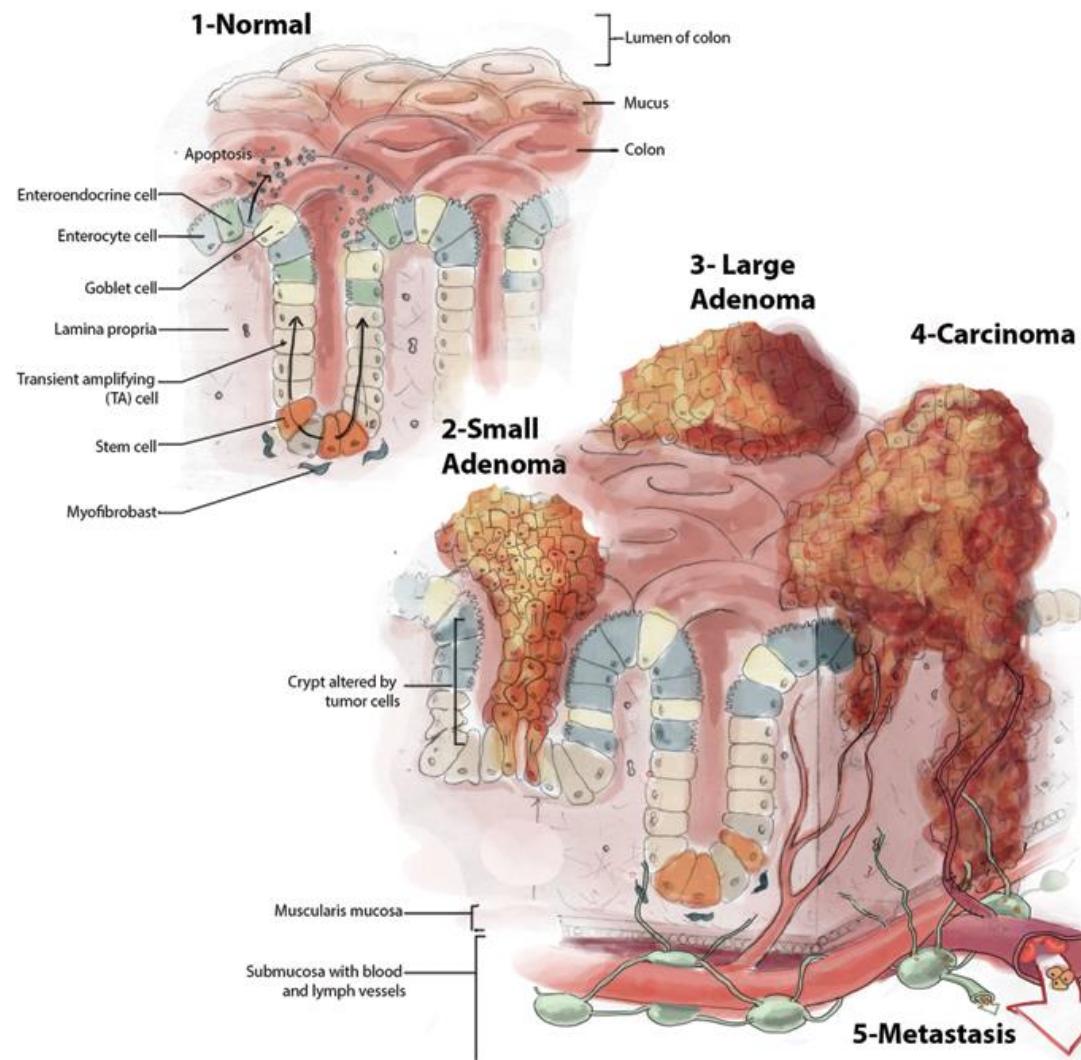


# The Role of the Microbiome in Colon Cancer

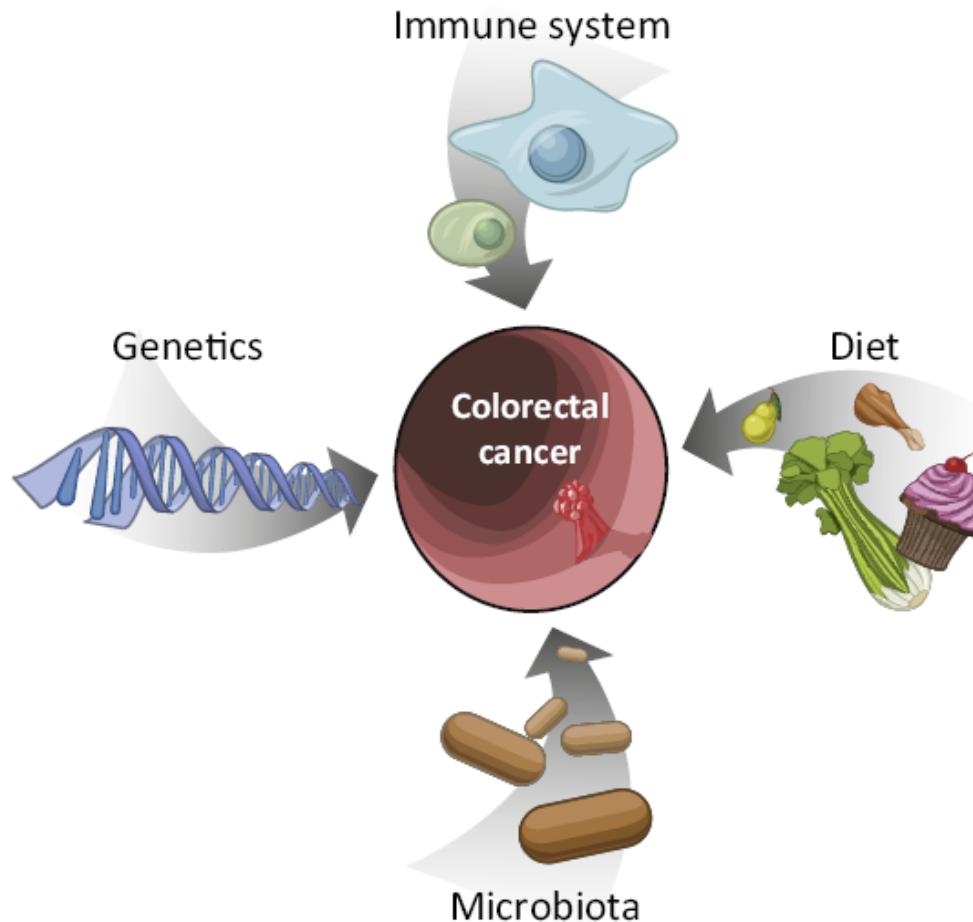


**Alberto Martin, PhD**  
**University of Toronto**

# Colorectal Cancer (CRC)



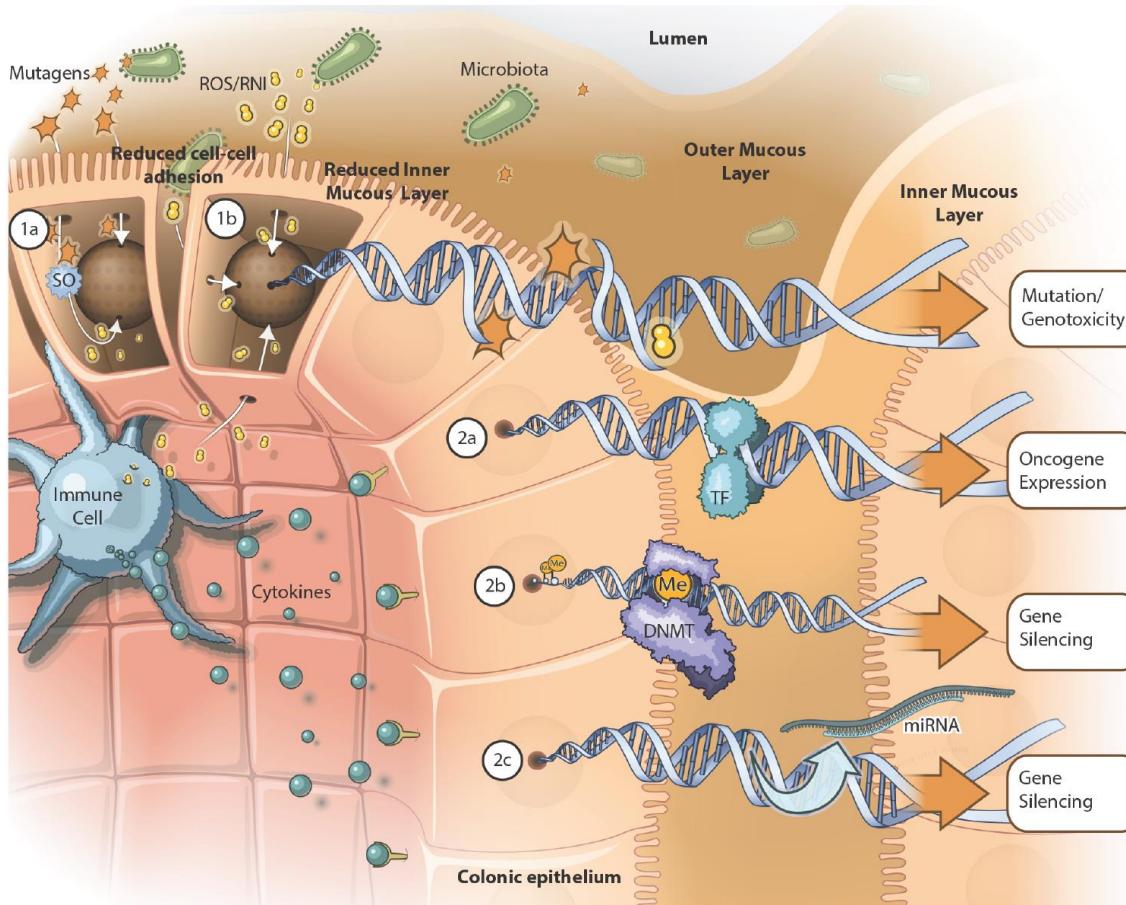
# Factors that promote CRC development



Trends in Molecular Medicine

# Potential origins of genetic mutations in Colorectal Cancer

1. Microbes (e.g. colibactin, BFT, CDT)
2. Inflammatory Cells (ROS, NO)
3. DNA repair Deficiency (MMR)

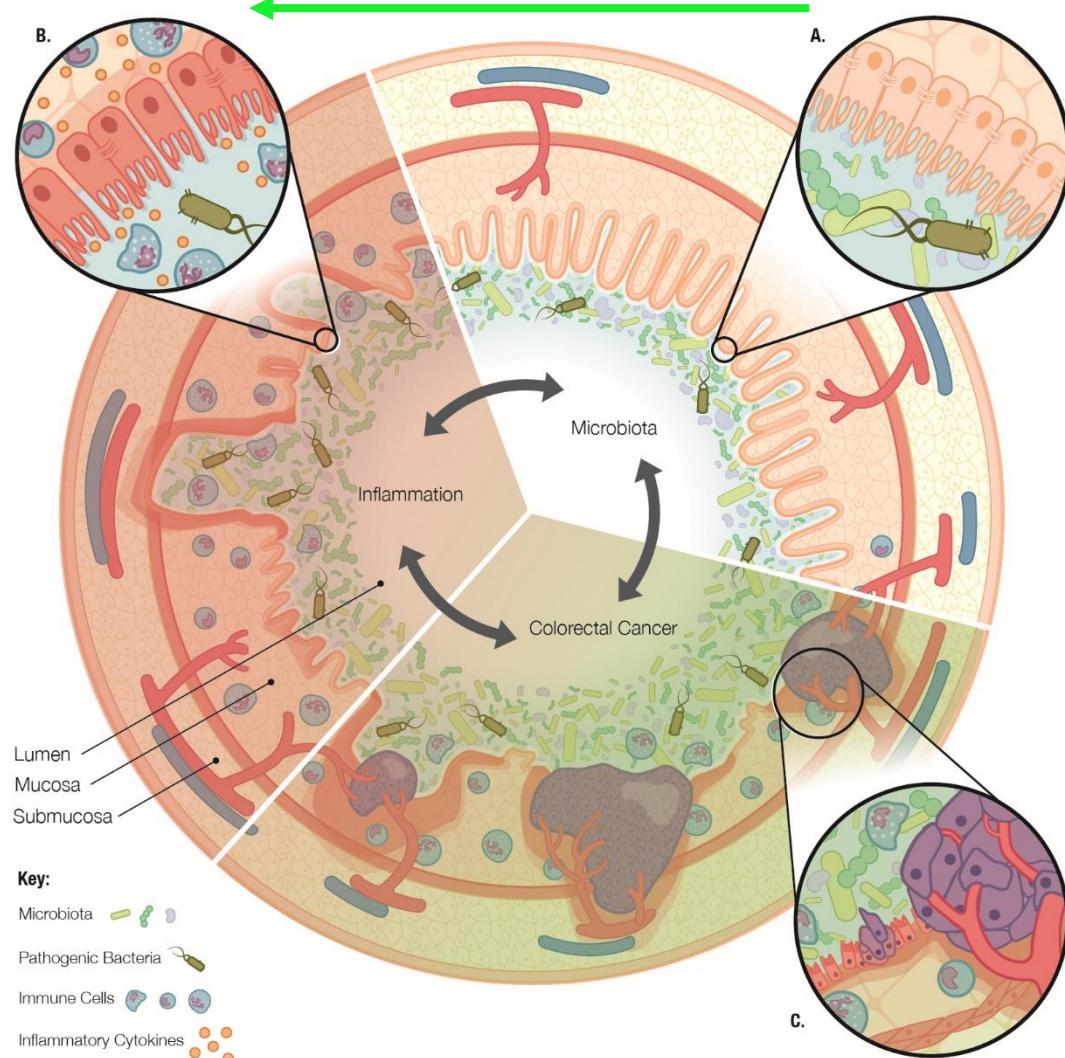


1. Colitis associated CRC (~5%)
2. Genetic non-colitis CRC (~95%)

*Escherichia coli NC101* (Jobin; Science 2012)  
*Enterotoxigenic Bacteroides fragilis* (Sears, Science 2018)  
*Helicobacter hepaticus* (Many papers)

## Inflammation

## Microbiota



## CRC

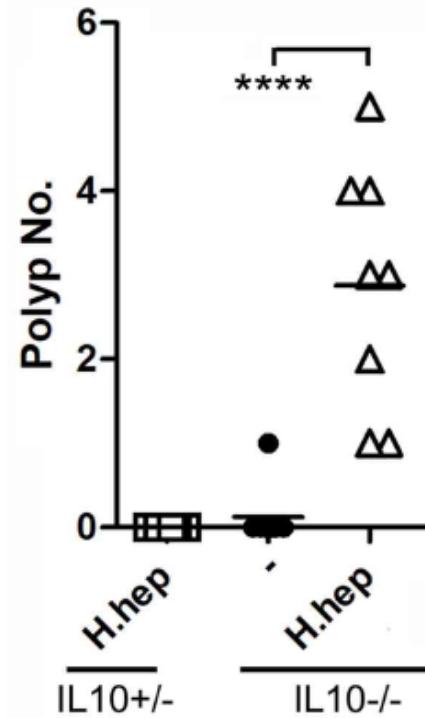
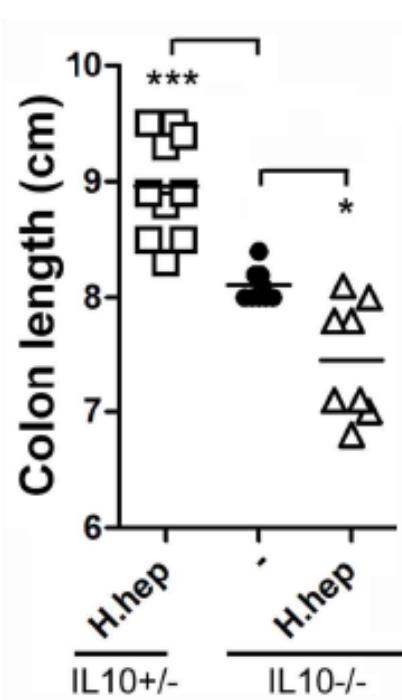
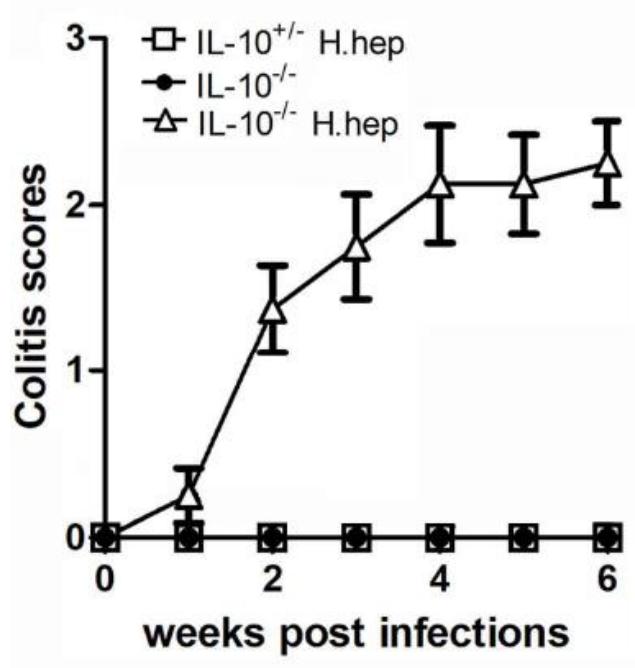
A mouse model for IBD

IL10-/-

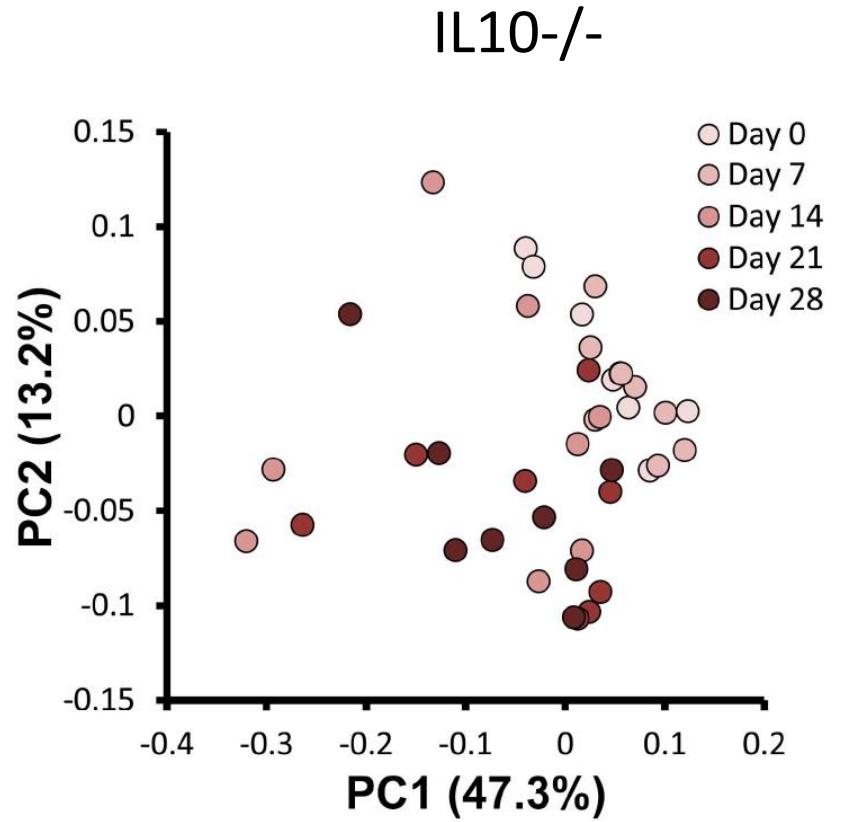


Develop 3 different models of CRC and assess  
whether the oncogenic mechanism is similar in  
all 3 models

## MODEL 1: *Helicobacter hepaticus* induces inflammation and CRC in IL10<sup>-/-</sup> mice



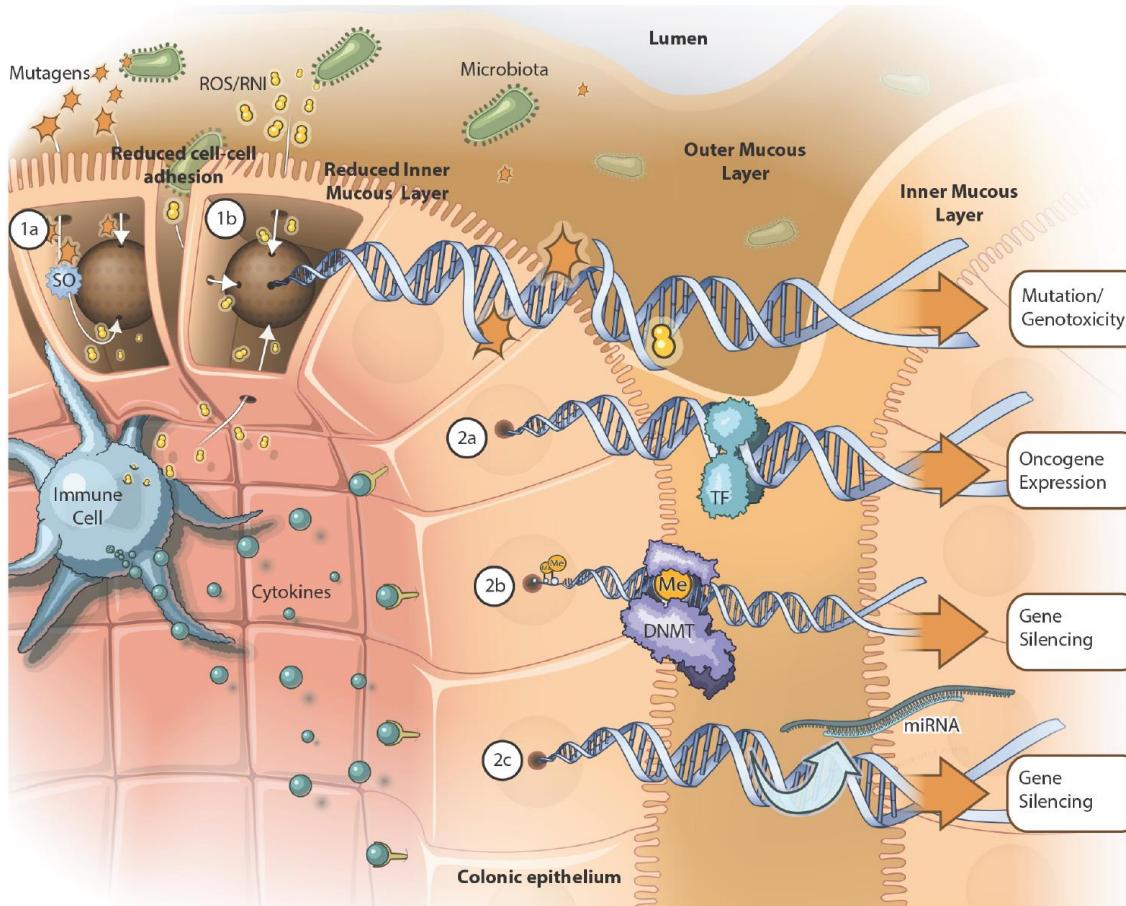
## MODEL 1: *Helicobacter hepaticus* induces dysbiosis in IL10<sup>-/-</sup> mice



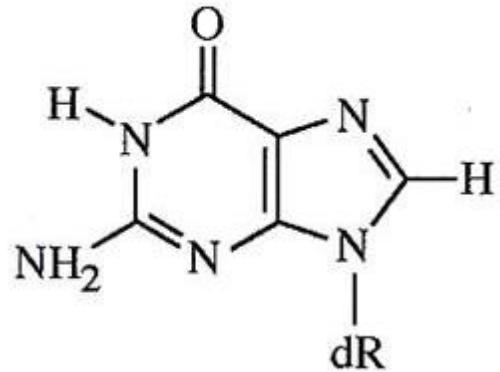
How does sustained inflammation lead to CRC?

# Potential origins of genetic mutations in Colorectal Cancer

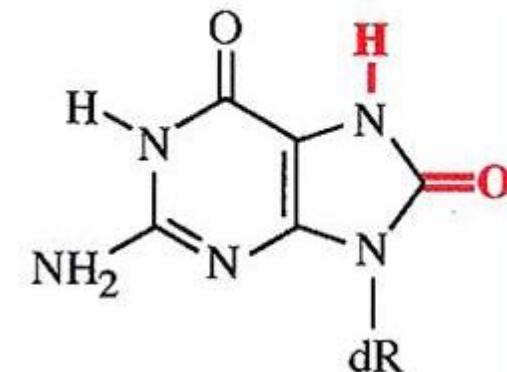
1. Microbes (e.g. colibactin, BFT, CDT)
2. Inflammatory Cells (ROS, NO)
3. DNA repair Deficiency (MMR)



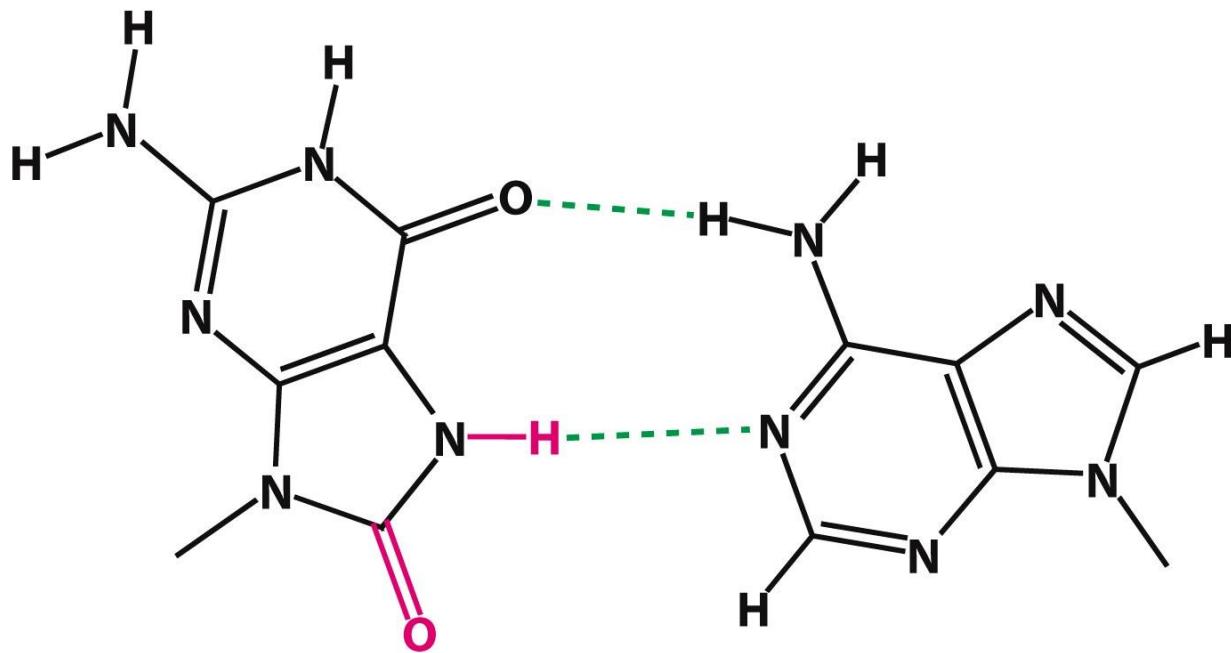
**guanine**



**8-oxoguanine**

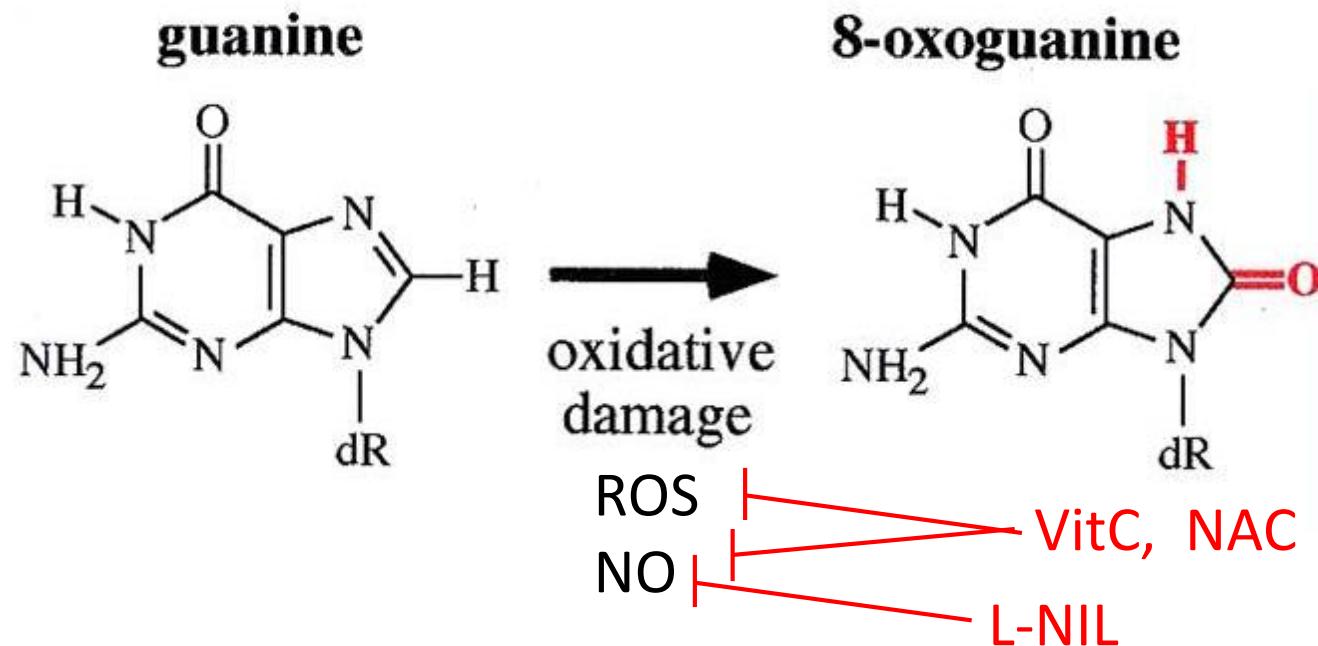


oxidative  
damage  
ROS  
NO



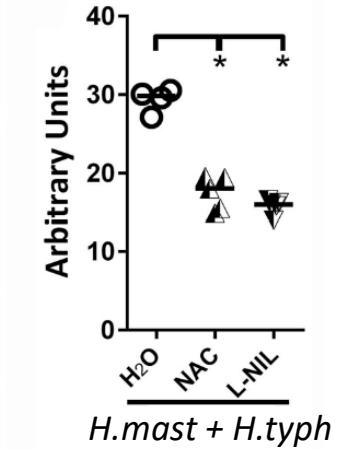
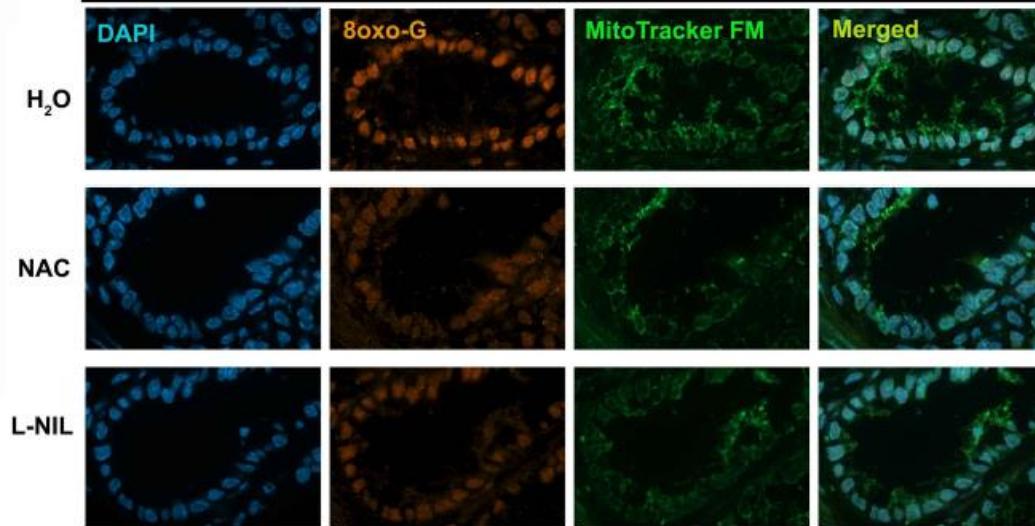
**8-Oxoguanine**

**Adenine**

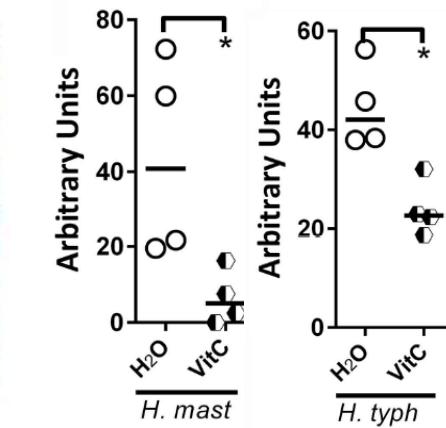
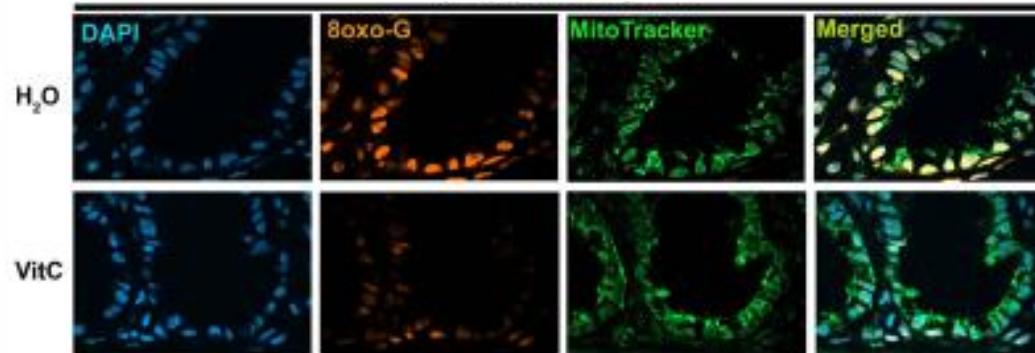


# MODEL 1: Antioxidants and L-NIL reduce oxidative DNA damage in *Helicobacter*-infected IL10<sup>-/-</sup> mice

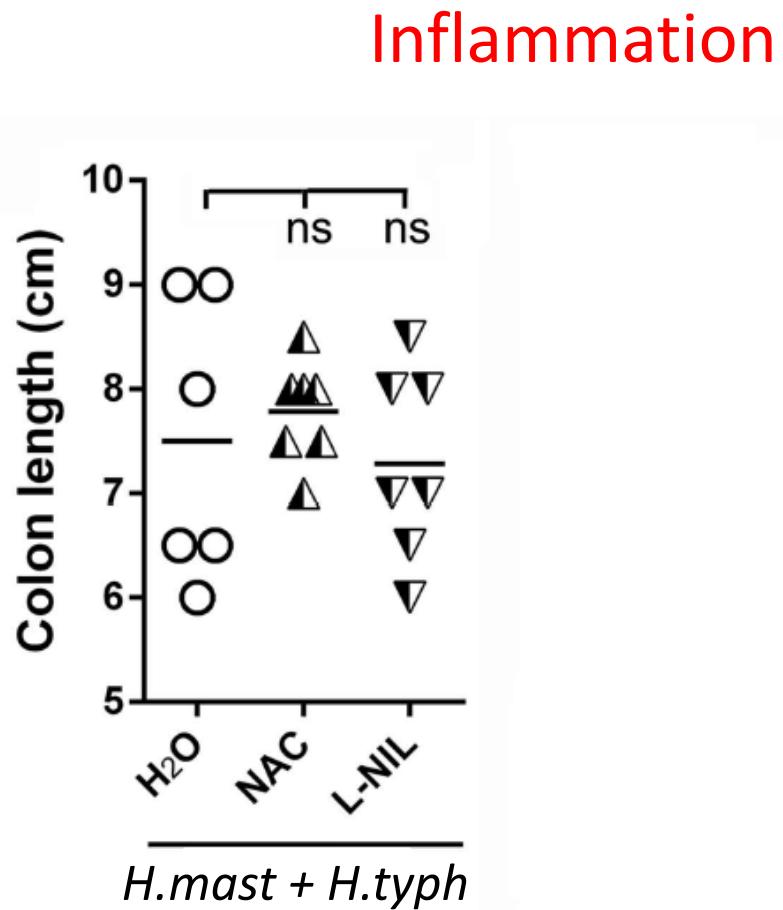
*H. mastomyrinus + H. typhlonius*



*H. mastomyrinus*

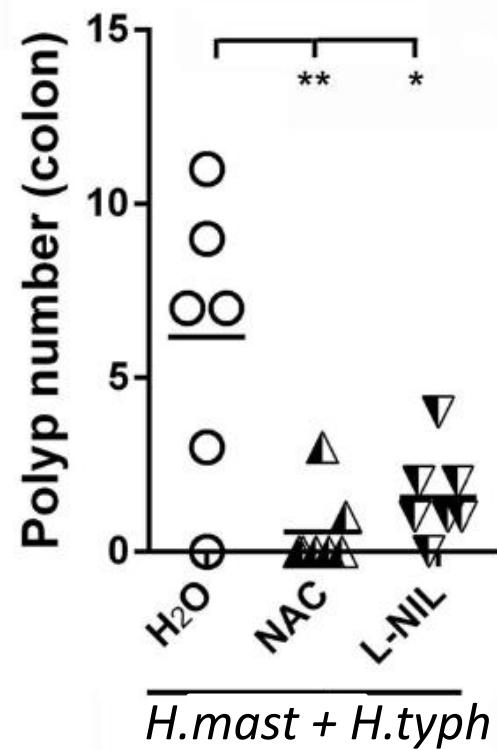


# MODEL 1: Antioxidants and L-NIL reduce CAC in *Helicobacter-infected IL10-/-* mice

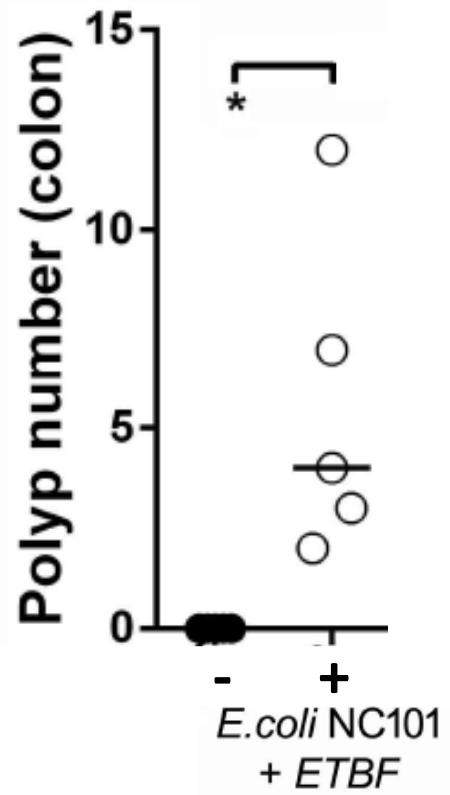


# MODEL 1: Antioxidants and L-NIL reduce CAC in *Helicobacter-infected IL10-/-* mice

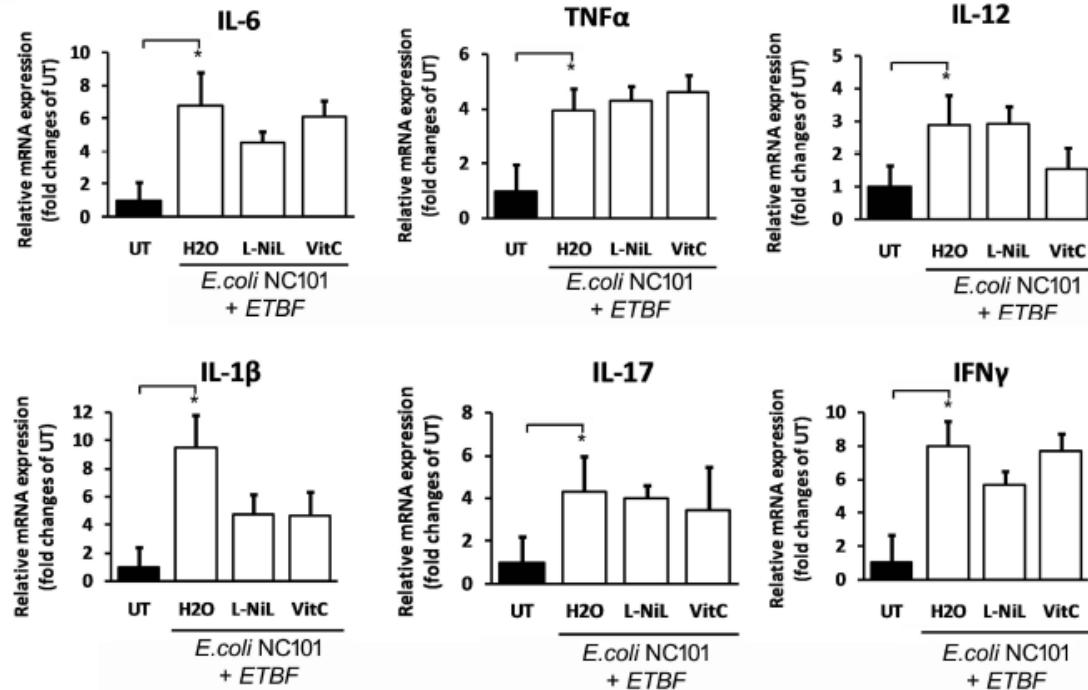
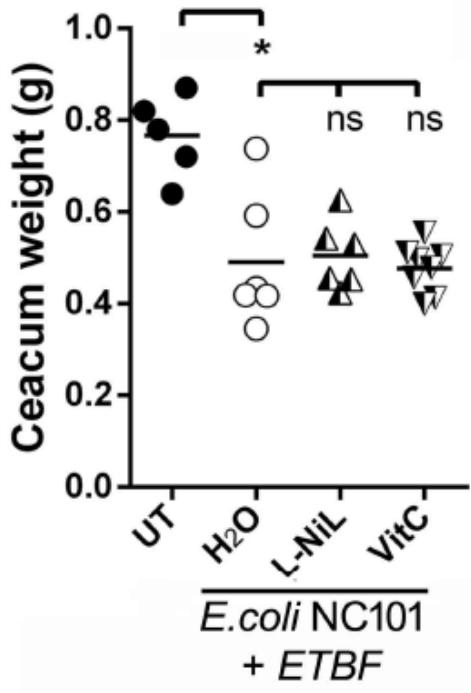
## Polyps



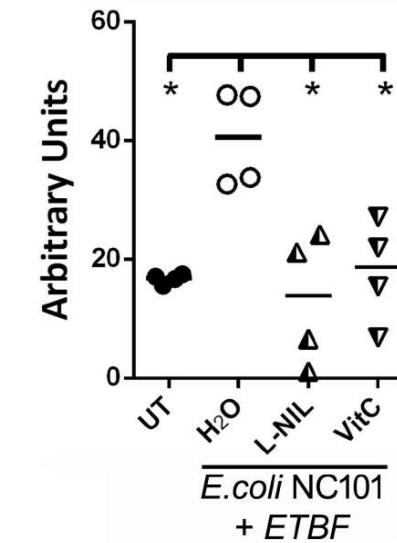
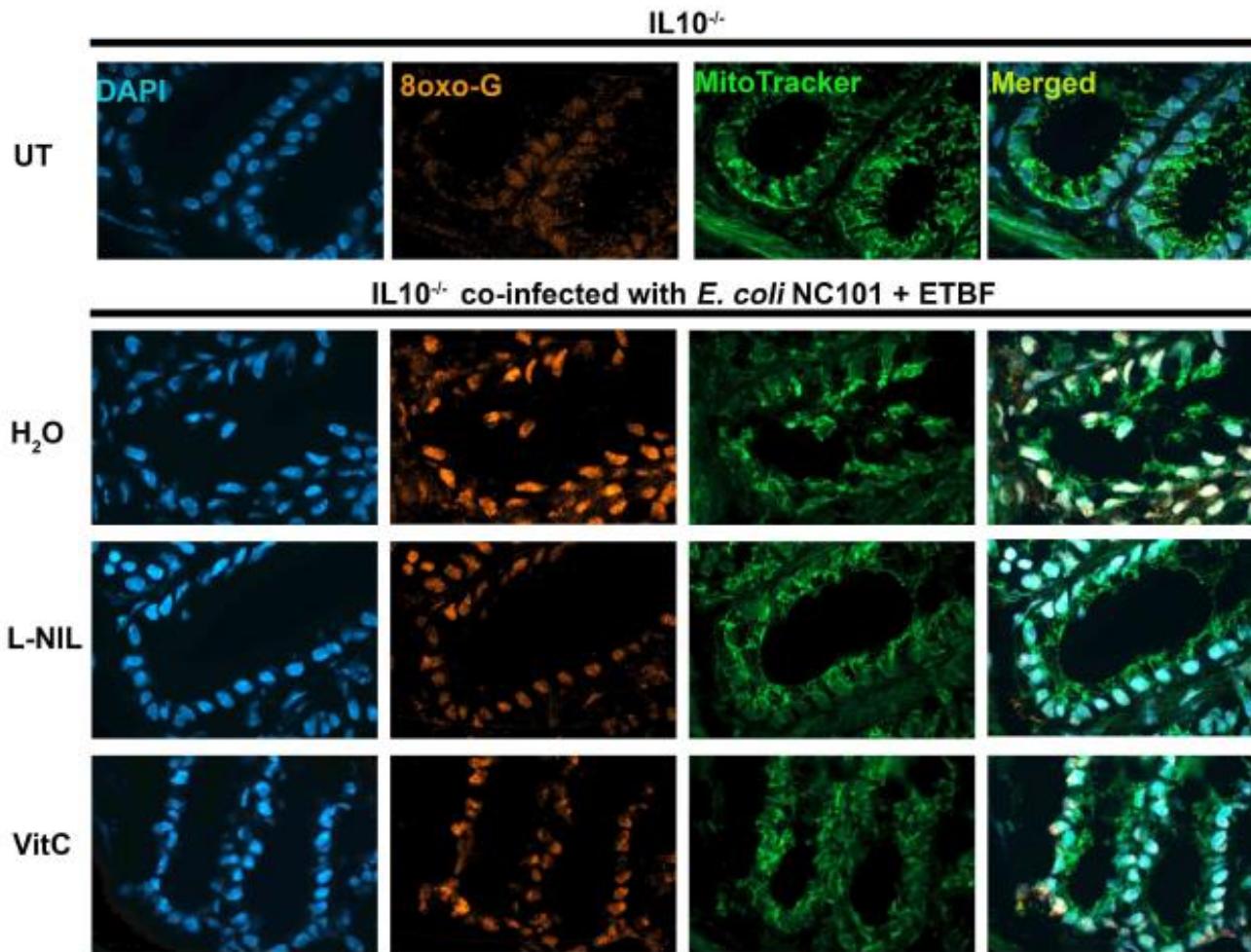
**MODEL 2: *E.coli* NC101 and Enterotoxigenic *B. fragilis* induces inflammation and CAC in IL10-/ mice**



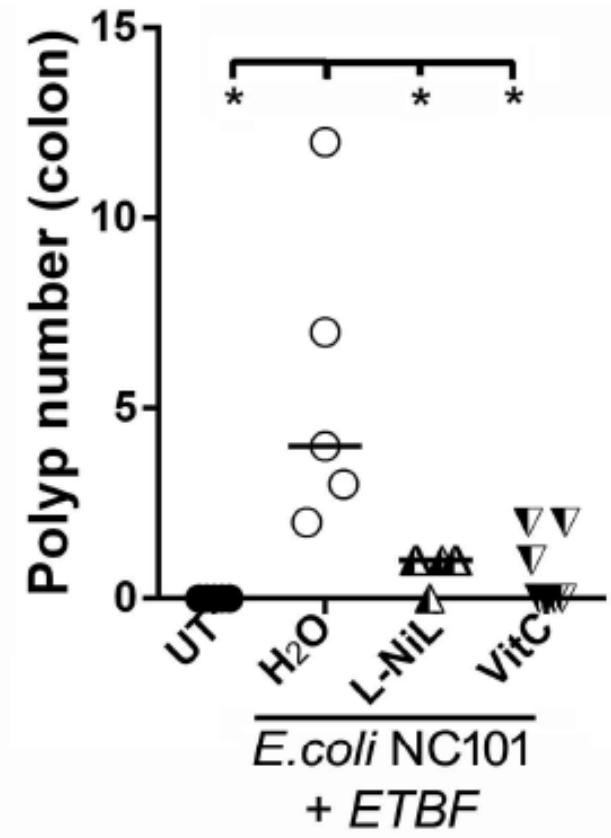
## MODEL 2: VitC and L-NIL do not reduce inflammation in *E.coli* NC101 and ETBF-infected IL10<sup>-/-</sup> mice



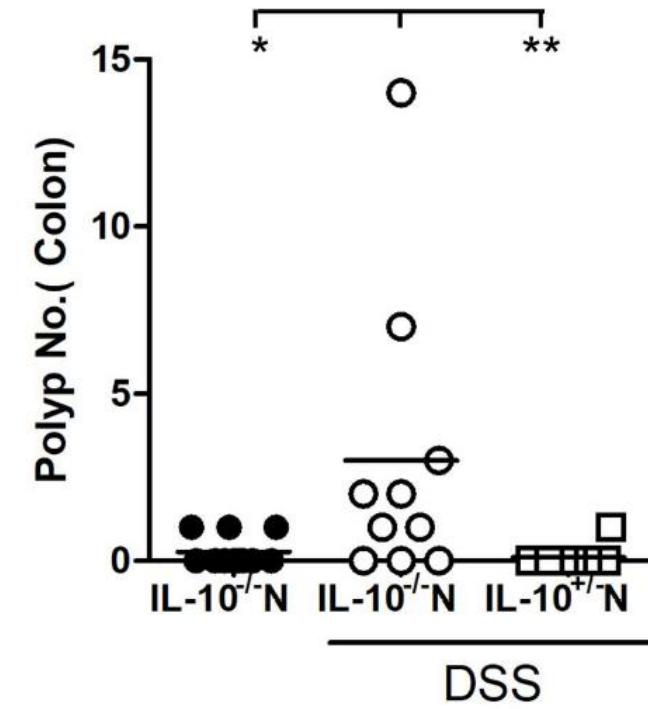
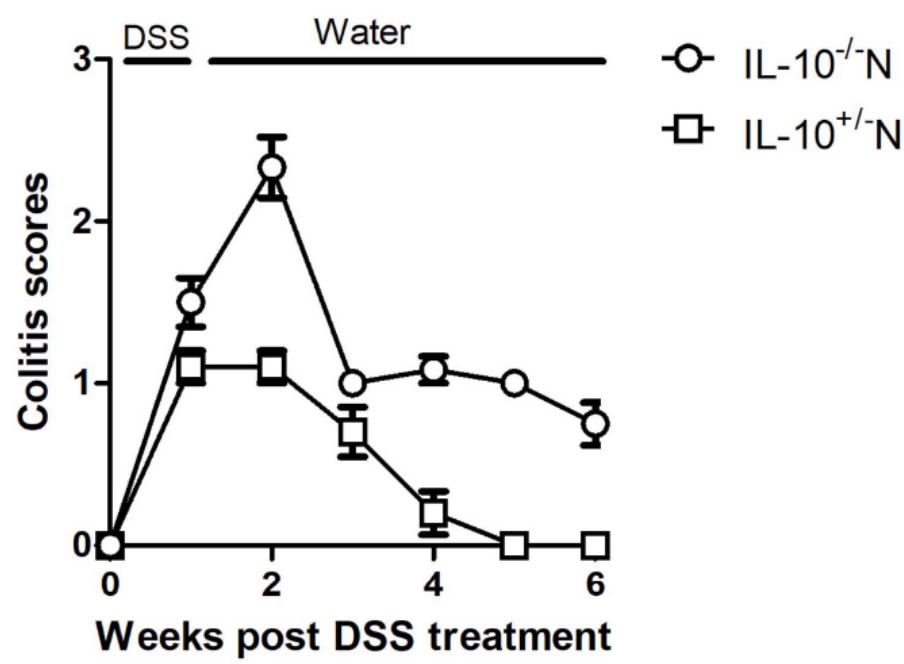
## MODEL 2: Reducing NO and ROS leads to reduced oxidative DNA damage



## MODEL 2: VitC and L-NIL reduce CAC in *E.coli* NC101 and ETBF-*infected* IL10-/- mice

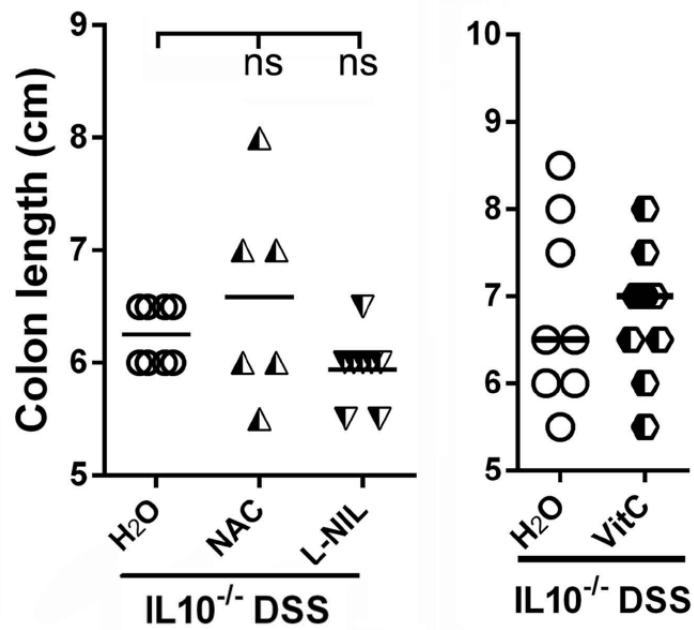


## MODEL 3: DSS induces inflammation and CRC in IL10<sup>-/-</sup> mice

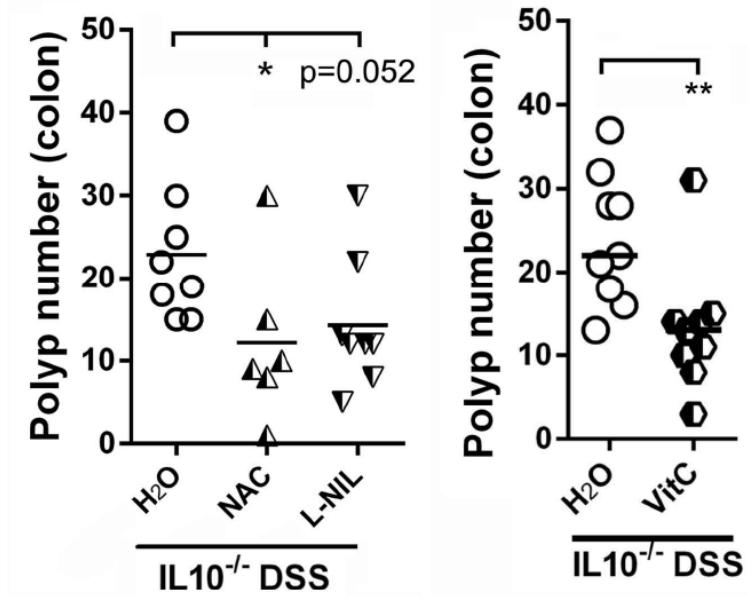


## MODEL 3: VitC and L-NIL reduce CAC in DSS-treated IL10<sup>-/-</sup> mice

### Inflammation



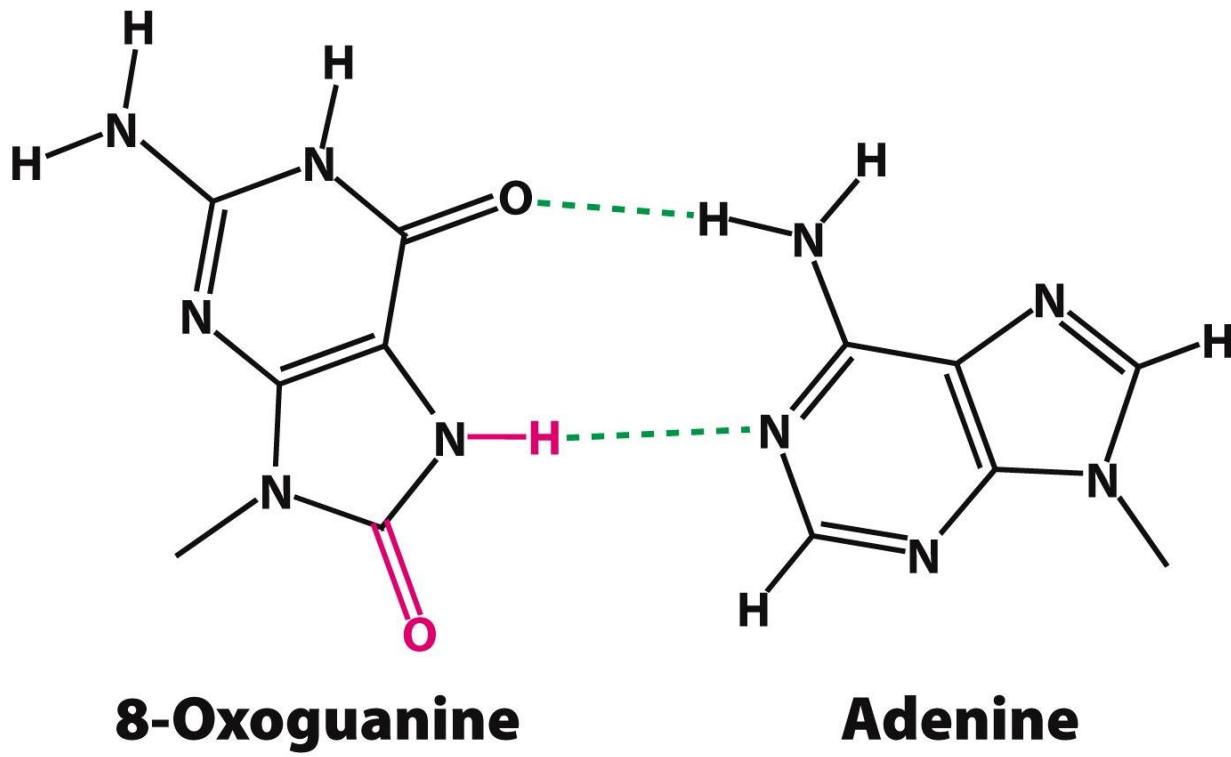
### Polyps



## **Conclusion 1:**

Reducing oxidative DNA damage in colitis  
models reduces Colitis-associated Colon Cancer

1. Colitis associated CRC (~5%)
2. Genetic non-colitis CRC (~95%)

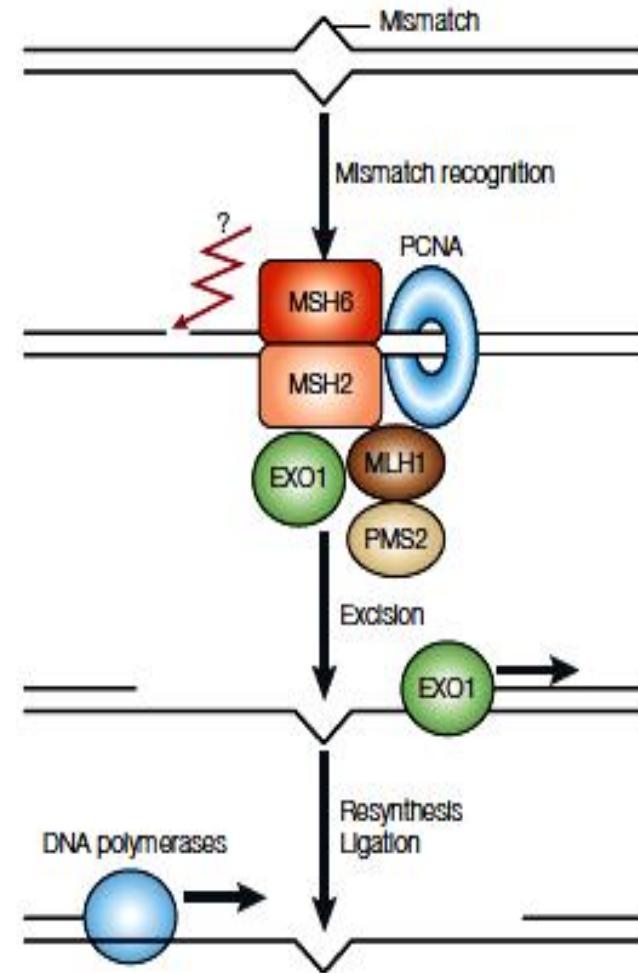


The mismatch repair pathway repairs  
incorporated 8-OxoG

# Mismatch repair (MMR)

## DNA Repair

- ❑ MMR pathway repairs errors made during DNA replication.



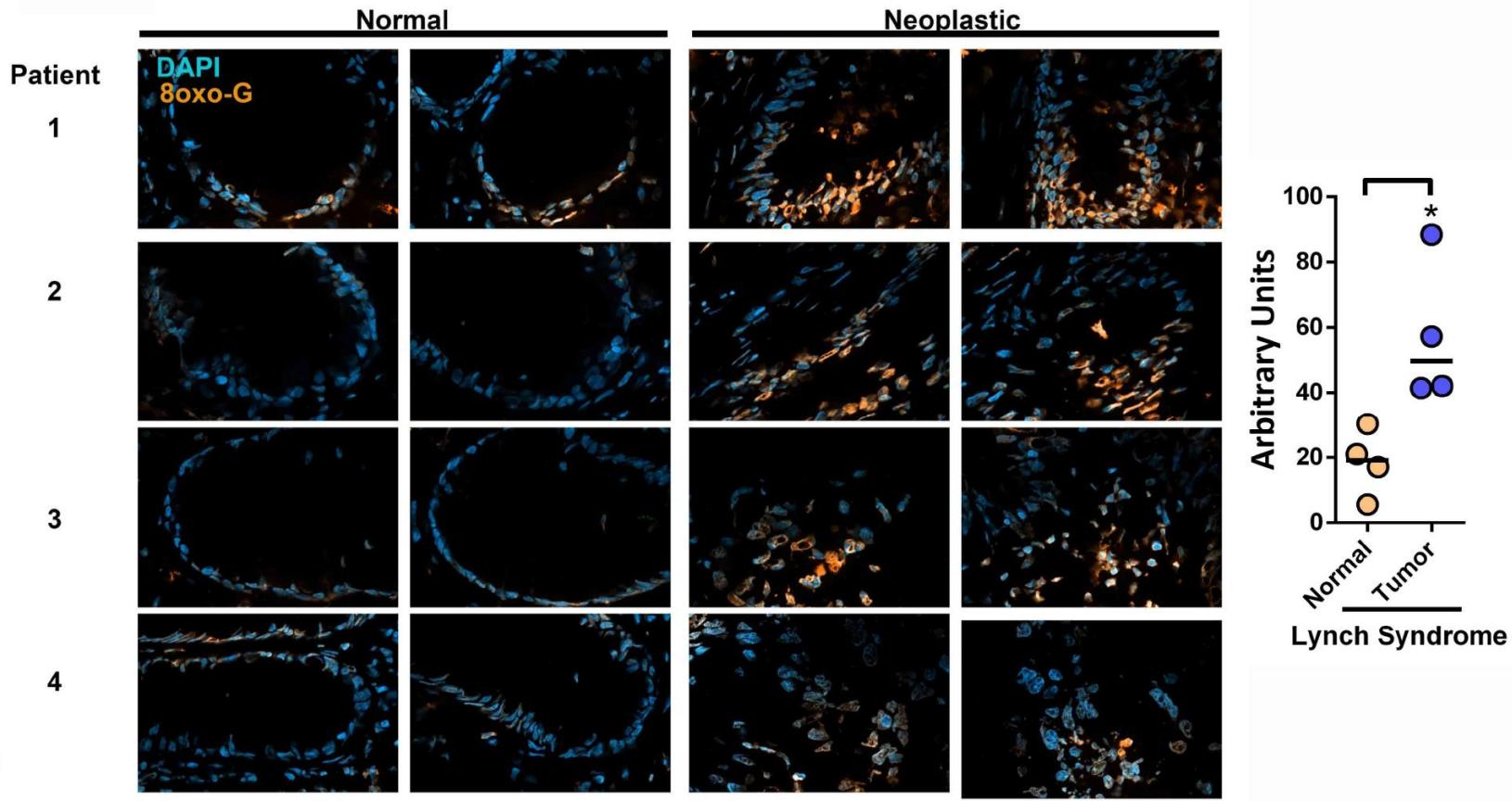
Martin & Scharff Nat Rev Imm 2002

# Mismatch Repair pathway and cancer

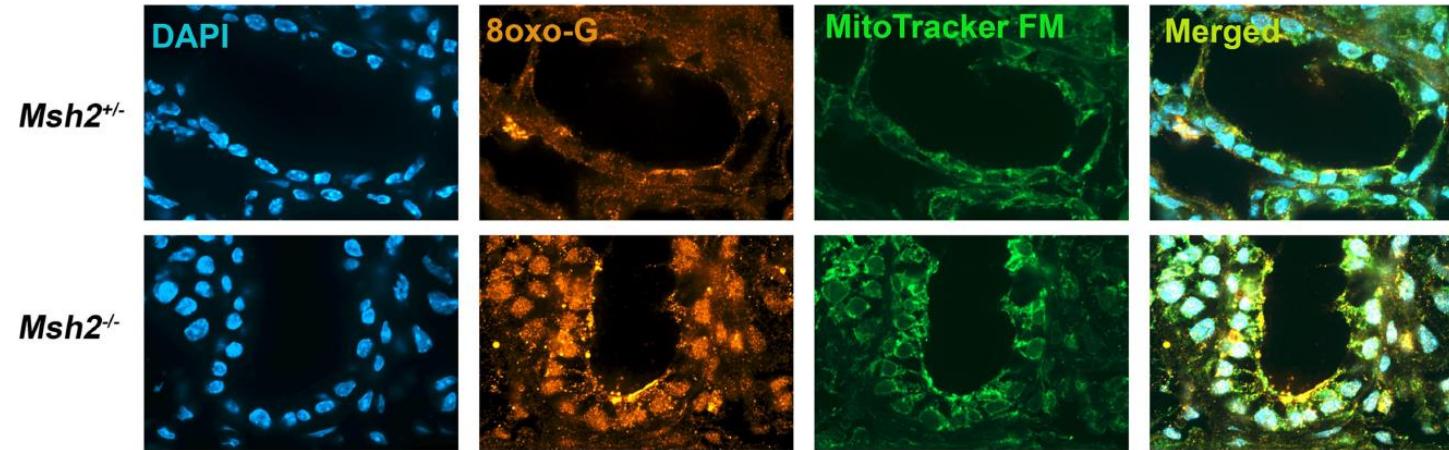
- ❑ Patients with germ line mutations in MMR genes (Lynch syndrome) are prone to develop CRC in 80% of the cases
- ❑ ~15% of all sporadic cancers harbour mutations in MMR genes

Is Oxidative DNA damage relevant in MMR-deficient models?  
(Microbiota induce CRC in MMR deficient mice; Belcheva *Cell* 2014)

# Increased oxidative DNA damage in Lynch syndrome tumors

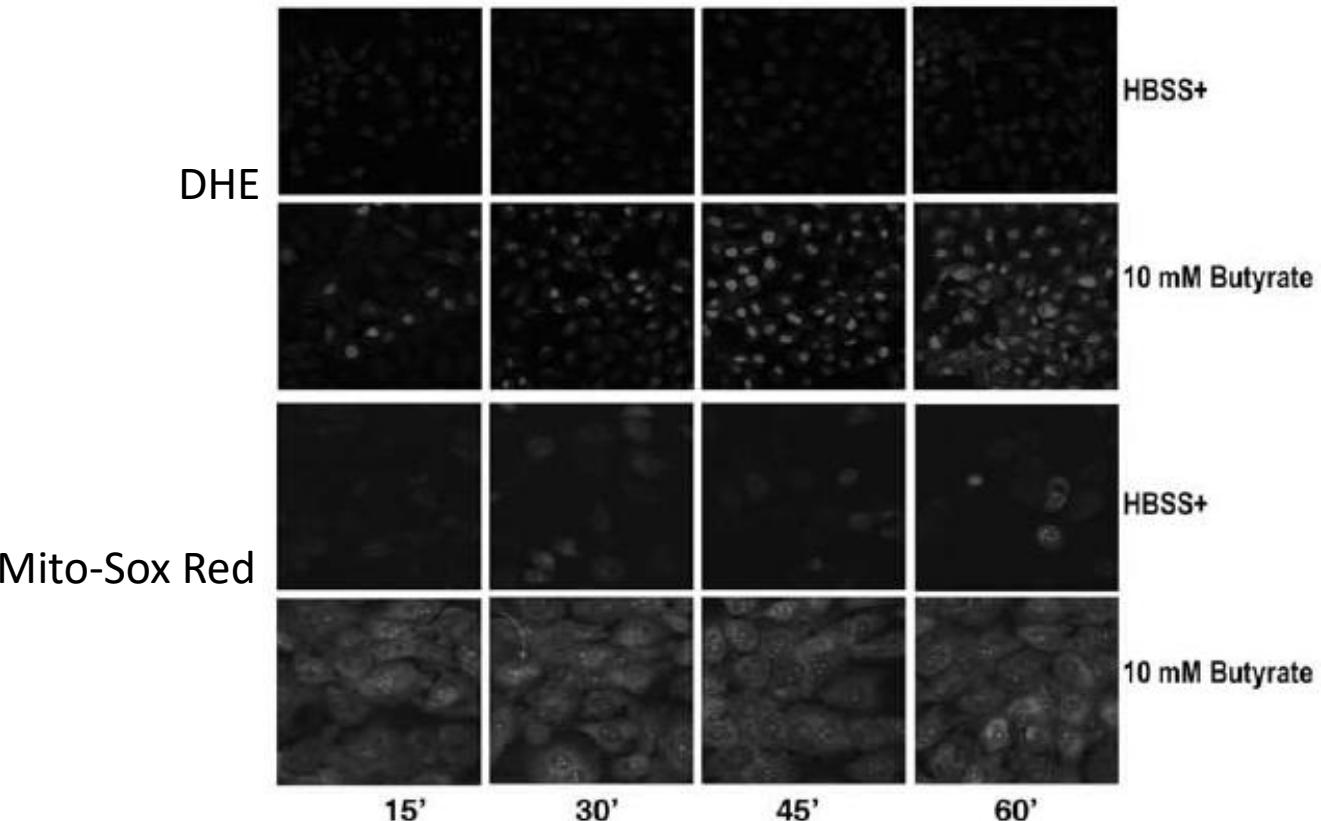


# Microbiota induces high levels of 8-oxoG in MMR-deficient colons



How do microbes induce high levels of oxidative DNA damage?

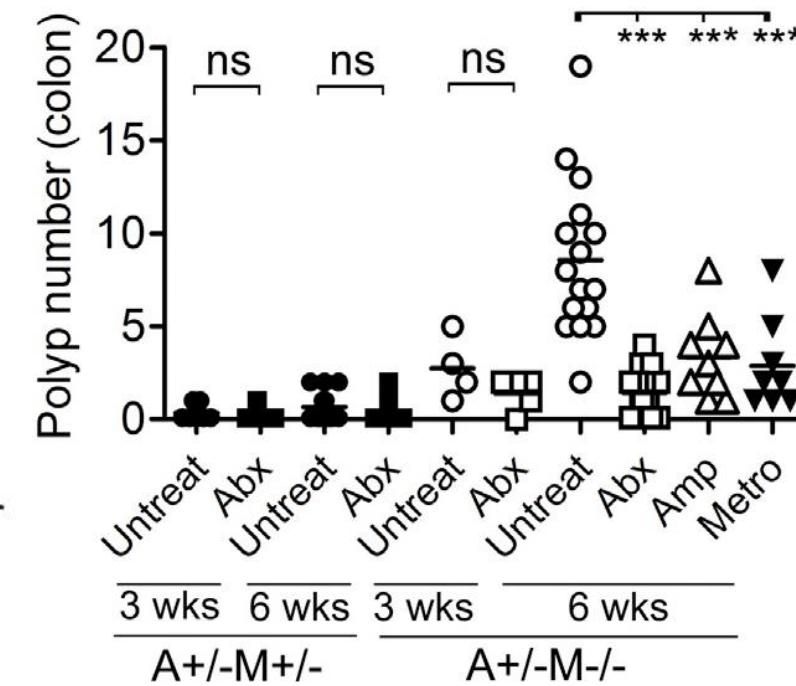
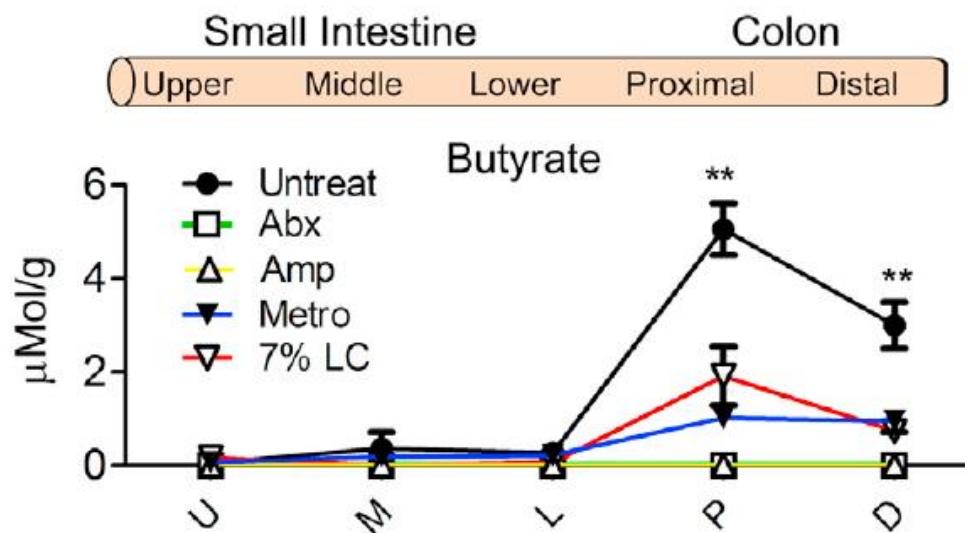
# Butyrate induces ROS in Rat small intestine epithelial cells



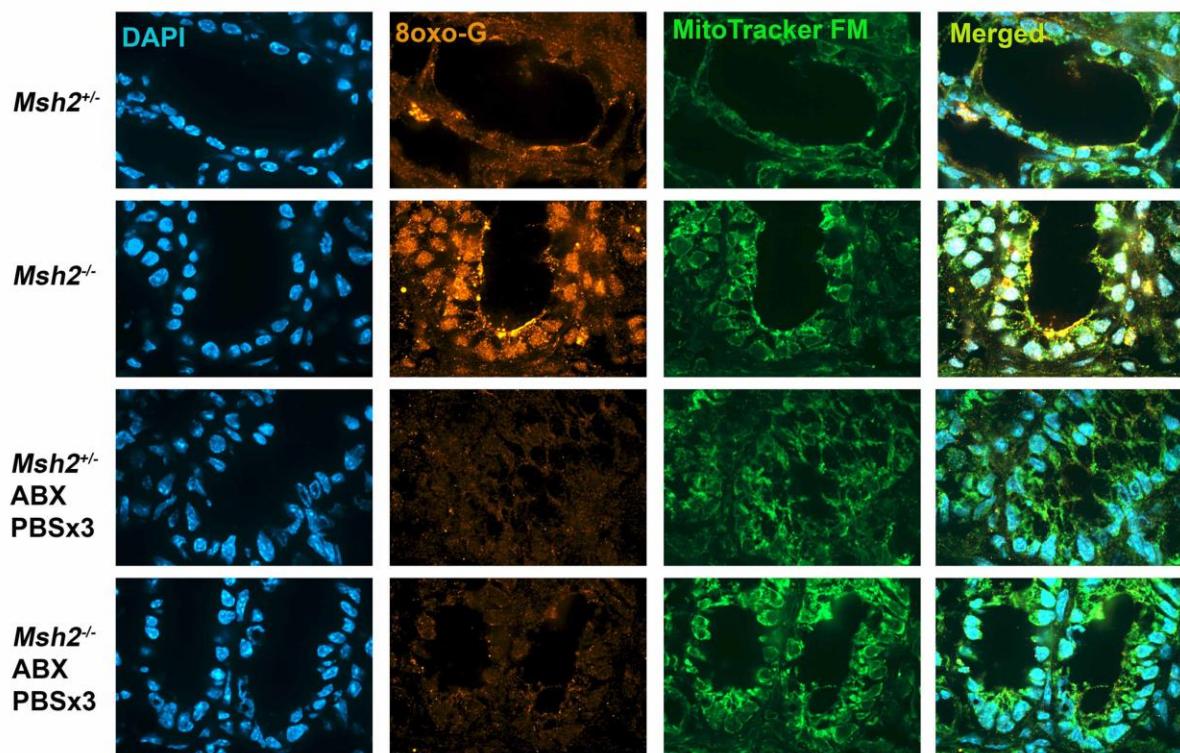
We confirmed this result

Kumar et al J. Immunology 2009

# Antibiotic treatment reduces butyrate in the GI track in mice



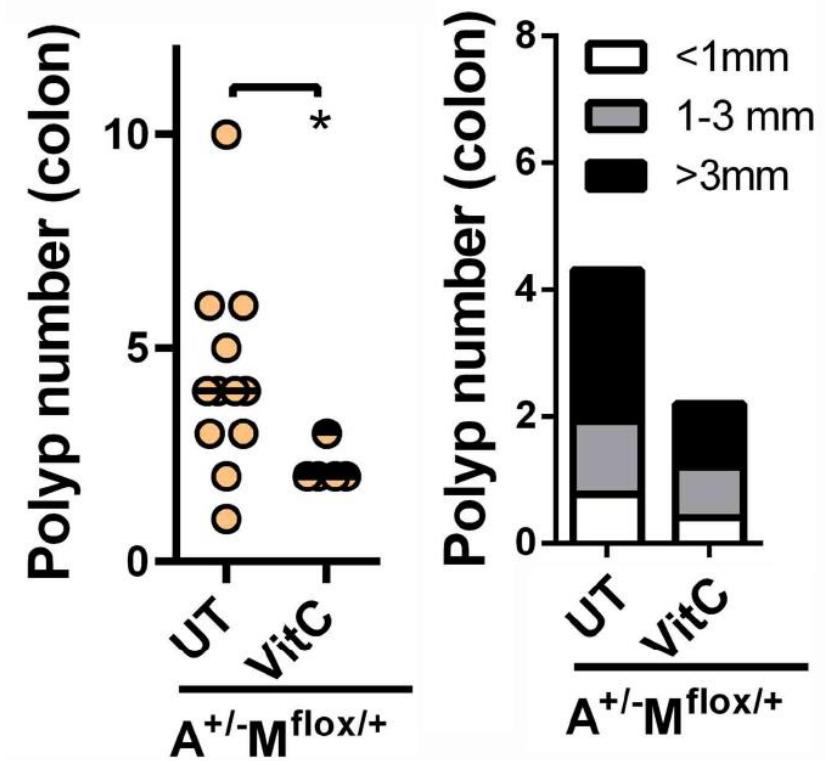
# Butyrate is sufficient to partially increase 8-oxoG in MMR-deficient colonocytes



# VitC reduces oxidative DNA damage in a Lynch syndrome mouse model

*Apc<sup>min/+</sup> Msh2<sup>flox/+</sup> Villin<sup>CRE</sup>*

# VitC reduces CRC in a Lynch syndrome mouse model



## **Conclusion 2:**

Microbial-induced oxidative DNA damage play causative roles in inflammatory and hereditary CRC models

- Potentially provides therapeutic avenues for these susceptible populations.



### The Martin lab:

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~~Dr. Antoaneta Belcheva~~  
Dr. Yann Malaise  
Dr. Yuqing Feng  
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Dr. Saurav Choudhury  
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