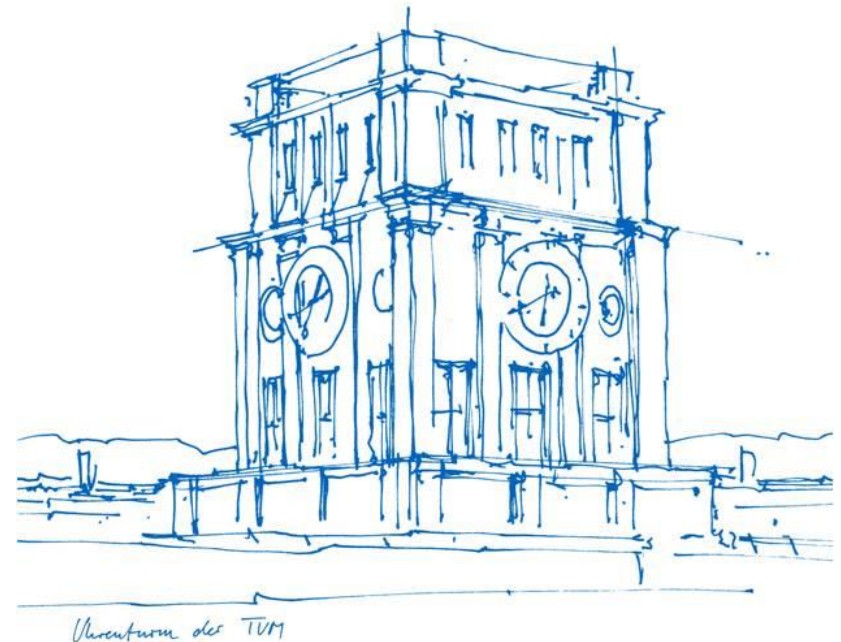
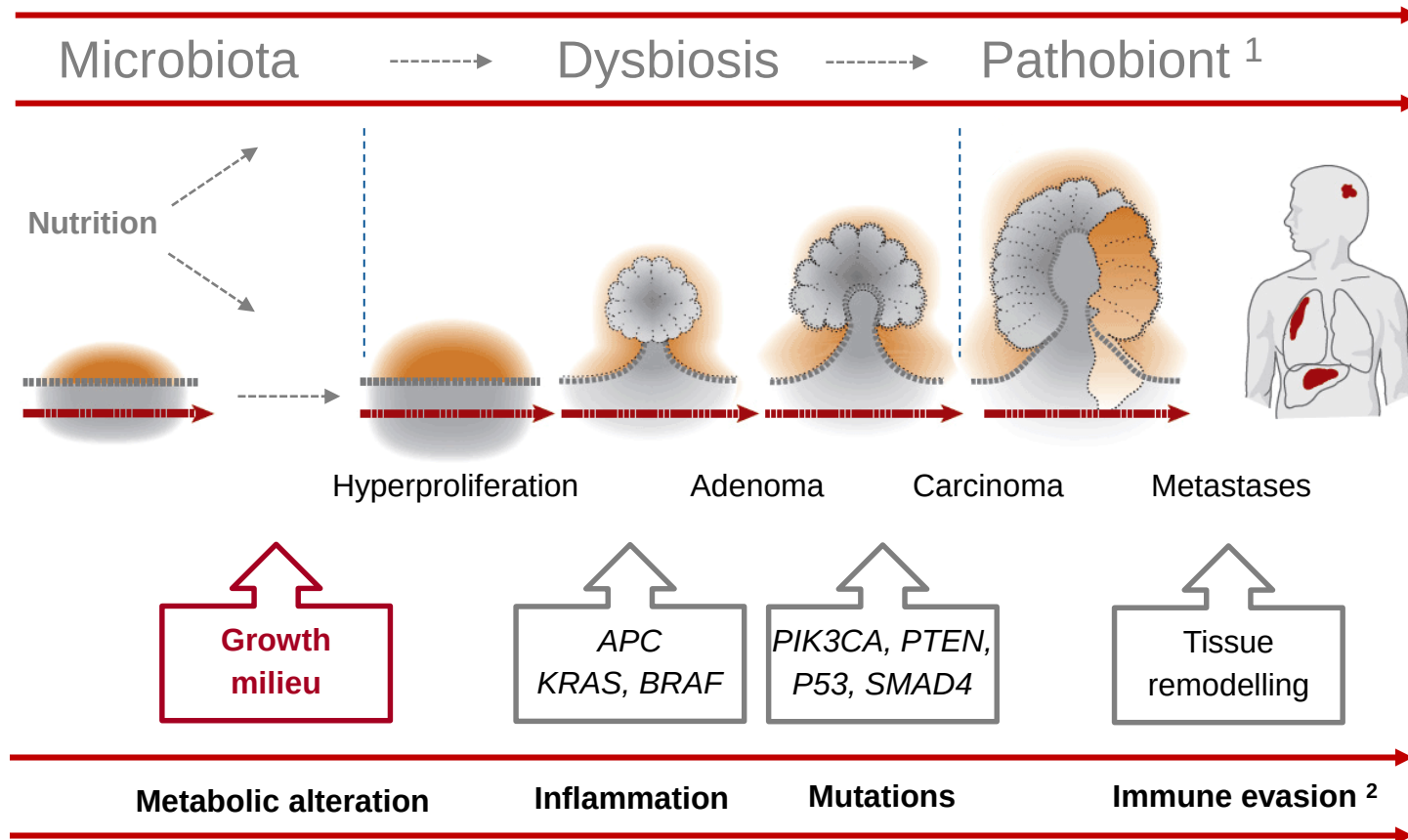


Cross-talk of the microbiome with the gut epithelium

Prof. Dr. Dirk Haller

Chair of Nutrition and Immunology
Director of ZIEL Institute for Food & Health
Technical University of Munich
www.nutrition-immunology.de

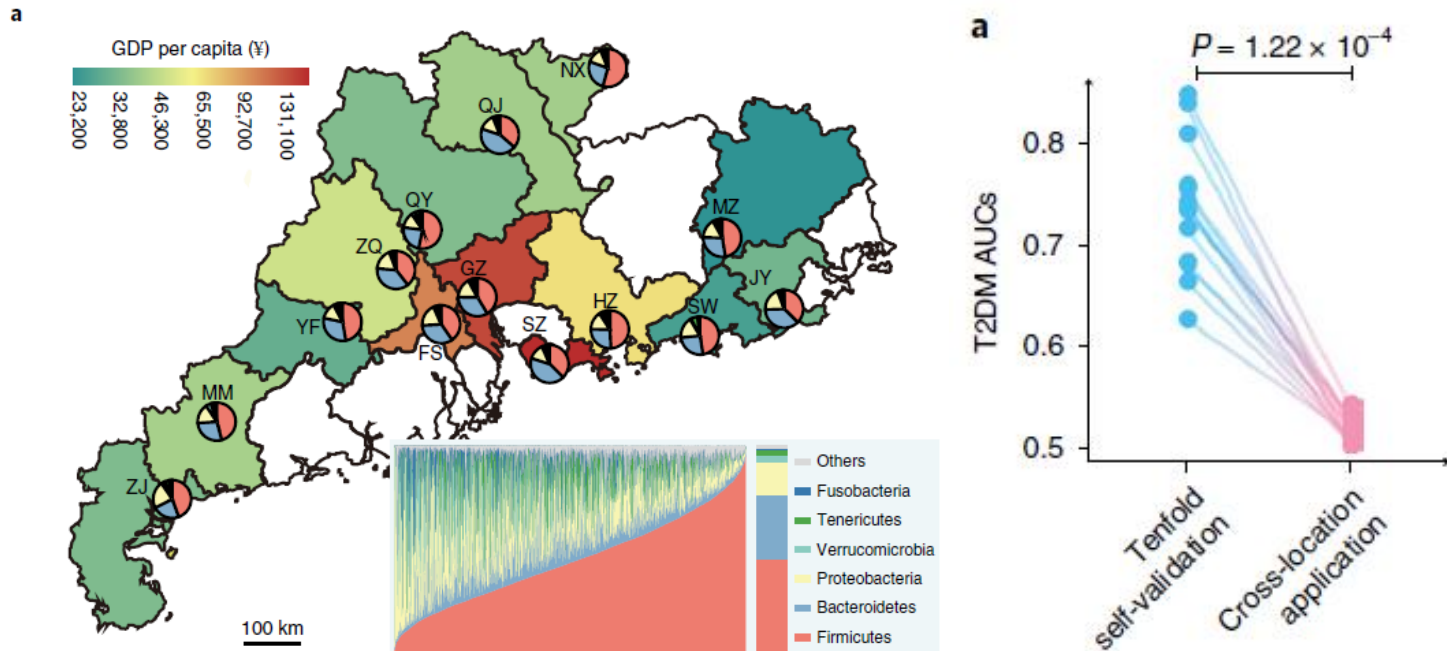




¹ Brennon and Garret 2016 Ann Rev Microbiol

² Hanahan and Weinberg 2011 Cell

Local environments dominate microbial signatures



LETTERS

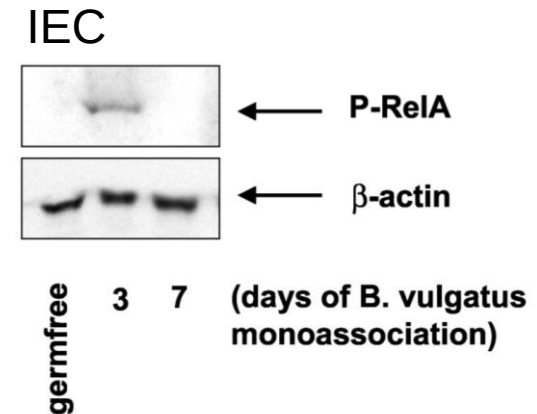
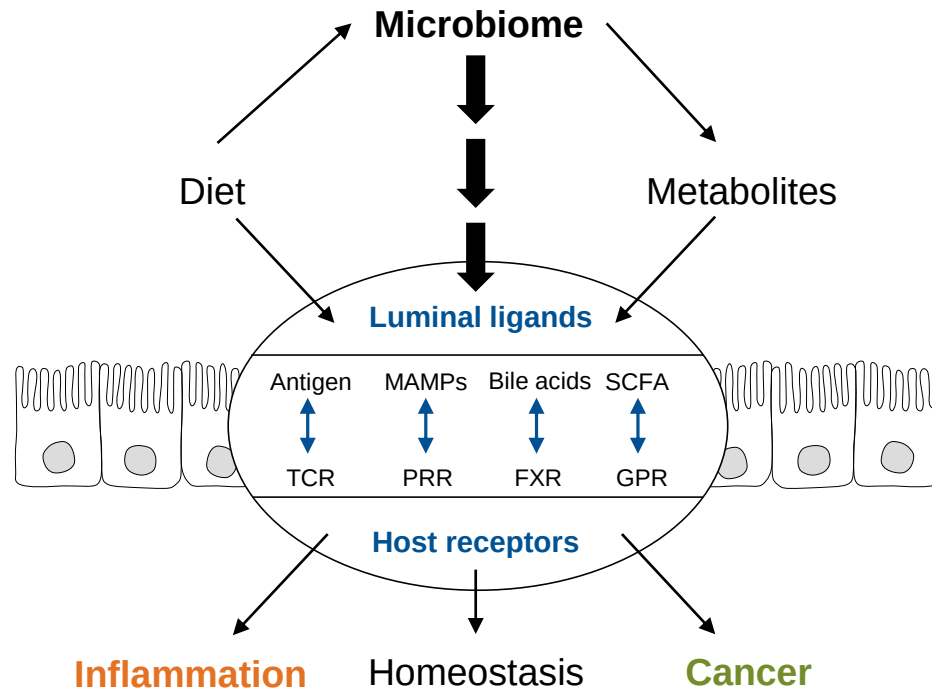
<https://doi.org/10.1038/s41591-018-0164-x>

nature
medicine

Corrected: Author Correction

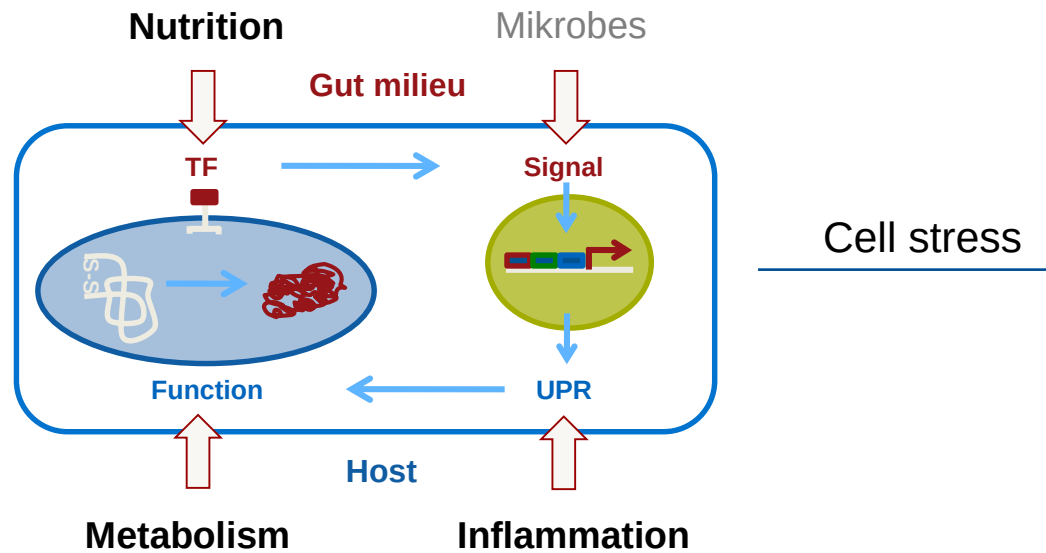
He et al. 2018

Regional variation limits applications of healthy gut microbiome reference ranges and disease models

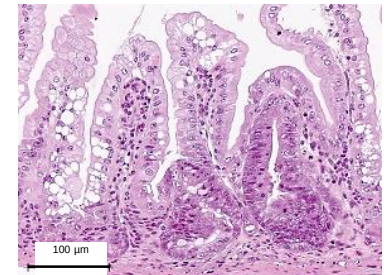


Haller et al. Gut 2000
Haller et al. J. Biol. Chem. 2002

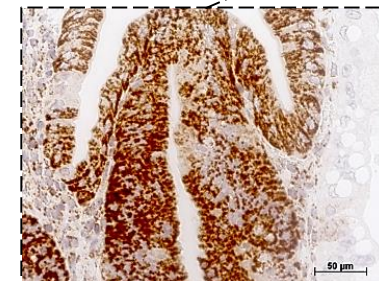
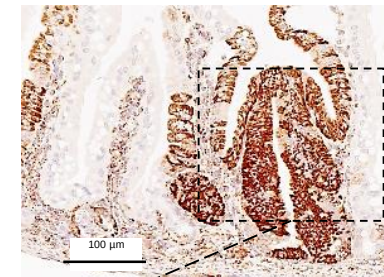
Hyperproliferative lesions under metabolic cell stress



H&E

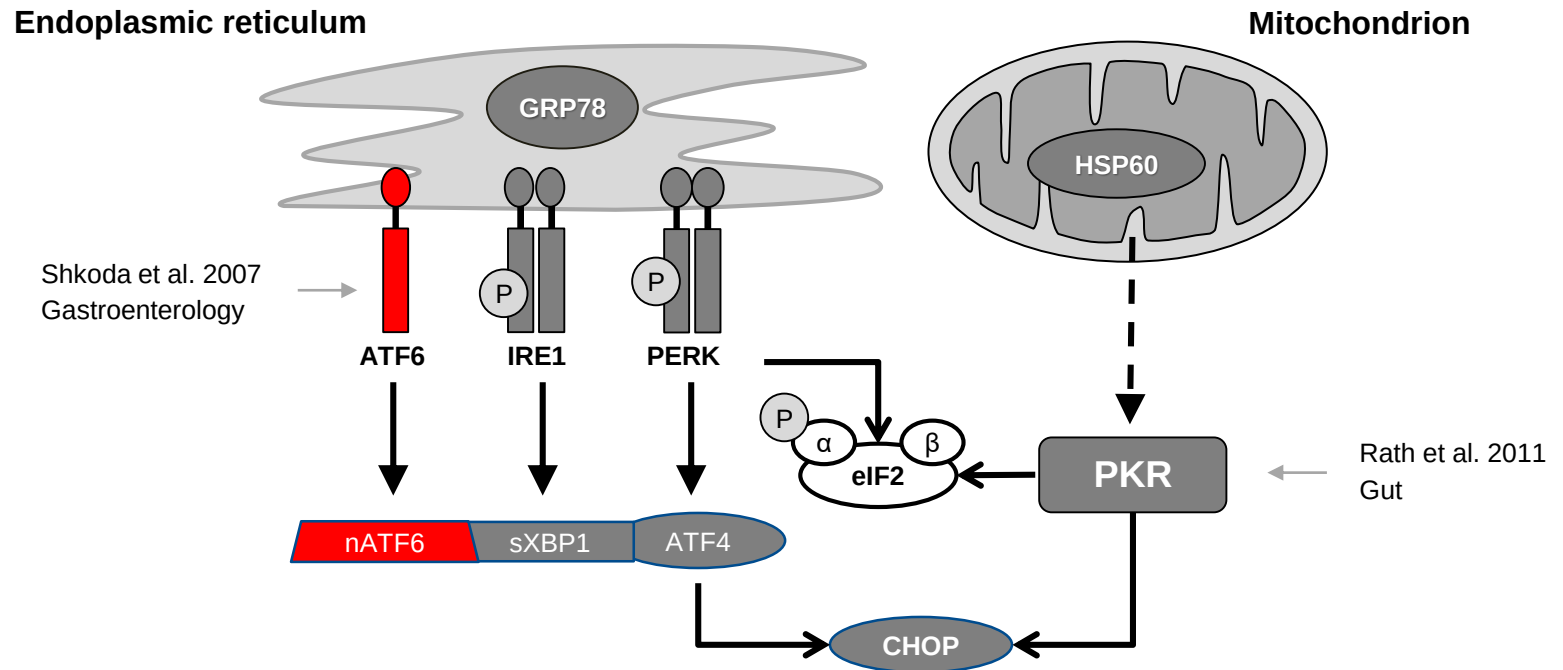


HSP60 IHC



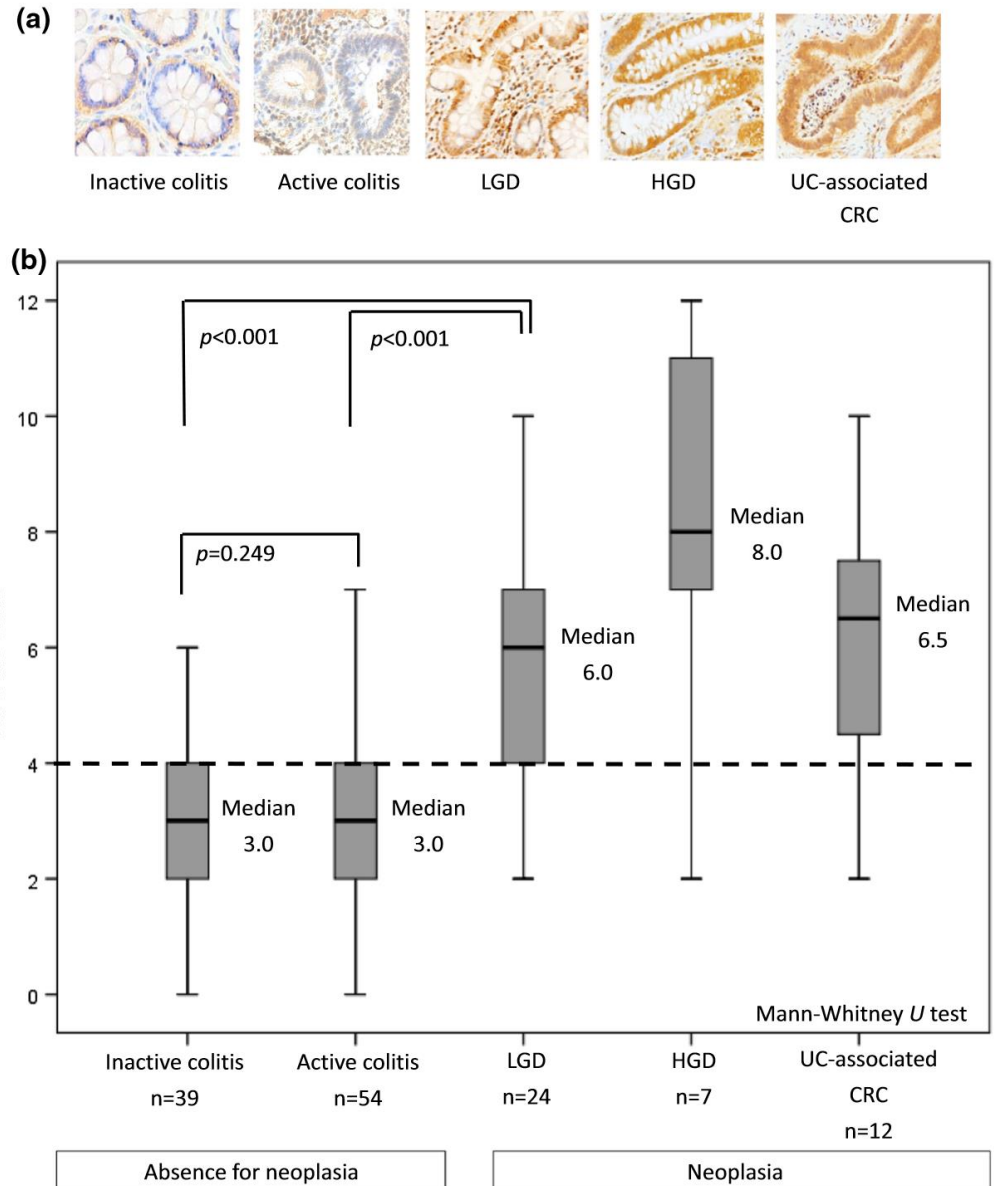
Berger, ..., Haller 2016 Nat. Commun.
Yuan, ..., Haller*, Heikenwälder* 2017 Cancer Cell
Rath, ..., Haller 2018 Nat. Rev. Gastroenterol. Hepatol.

Cell stress as cause or consequence in CRC

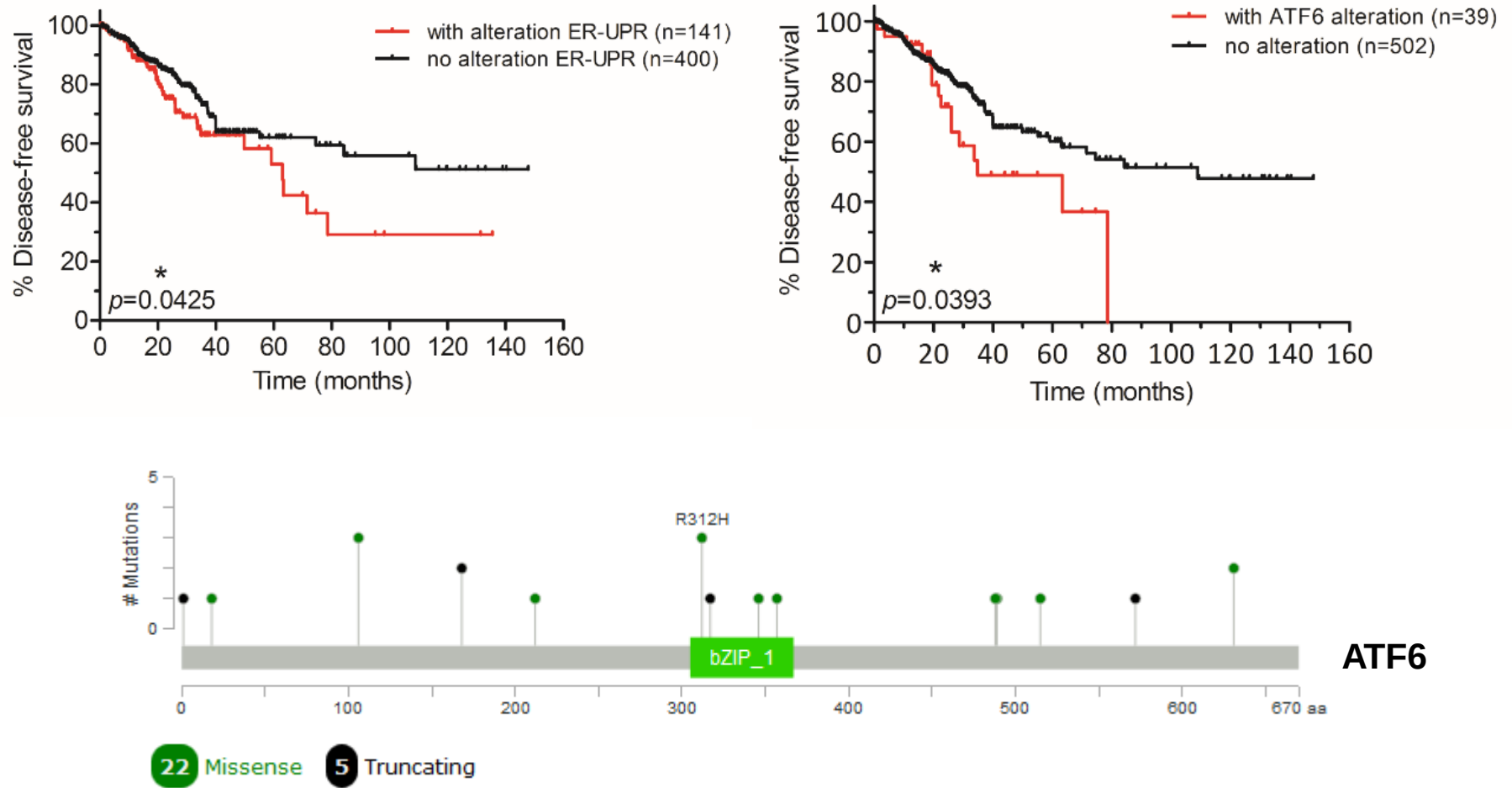


Expression of ATF6 as a marker of pre-cancerous atypical change in ulcerative colitis-associated colorectal cancer: a potential role in the management of dysplasia

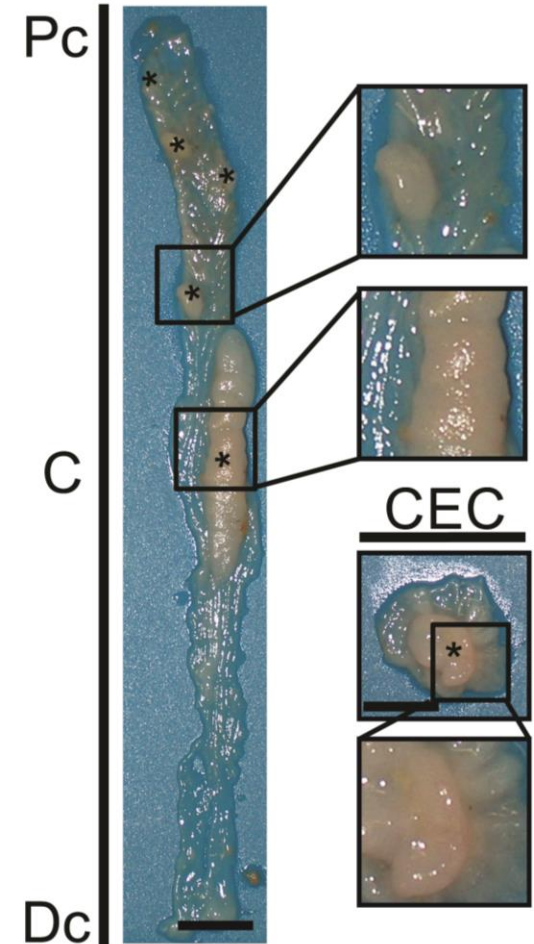
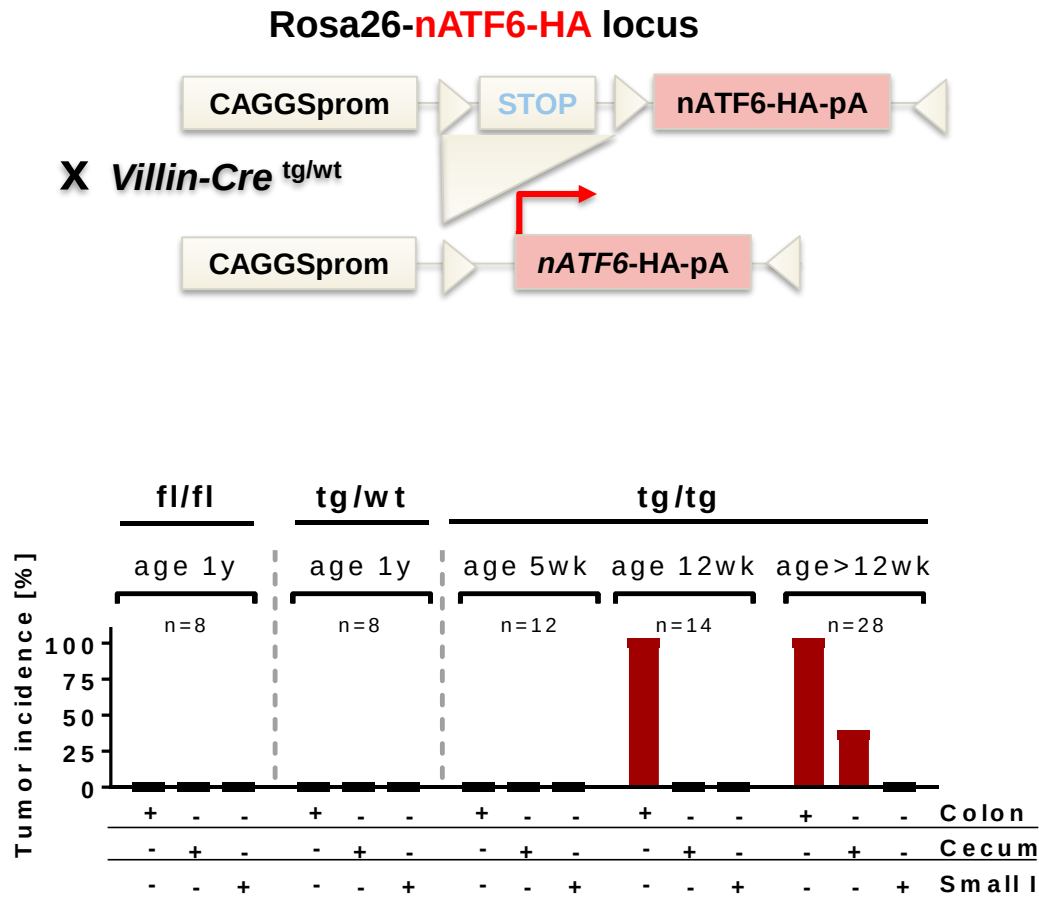
Marie Hanaoka¹ · Toshiaki Ishikawa² · Megumi Ishiguro³ · Michiyo Tokura¹ · Shinichi Yamauchi¹ · Akifumi Kikuchi¹ · Hiroyuki Uetake² · Masamichi Yasuno¹ · Tatsuyuki Kawano¹



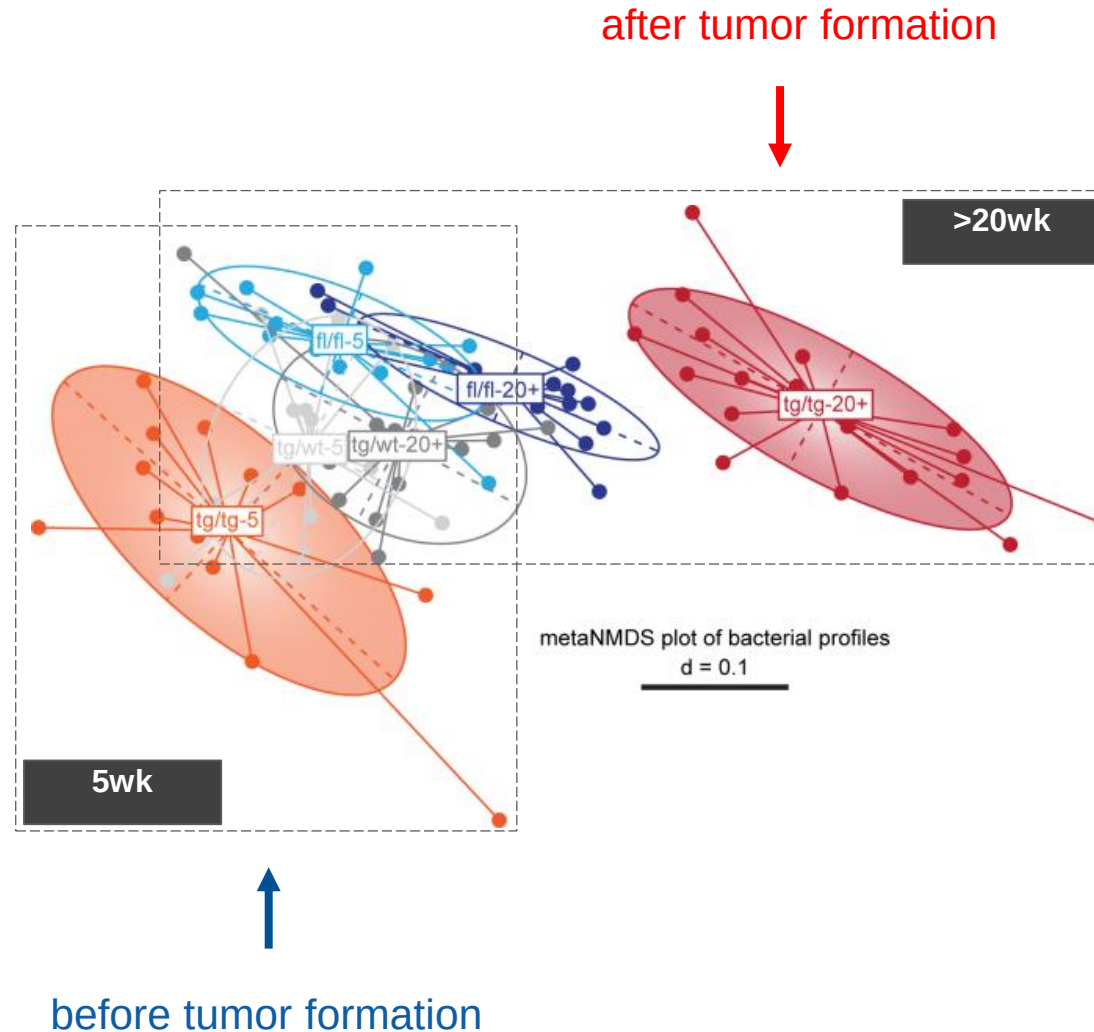
ATF6 as a potential new oncogenic driver



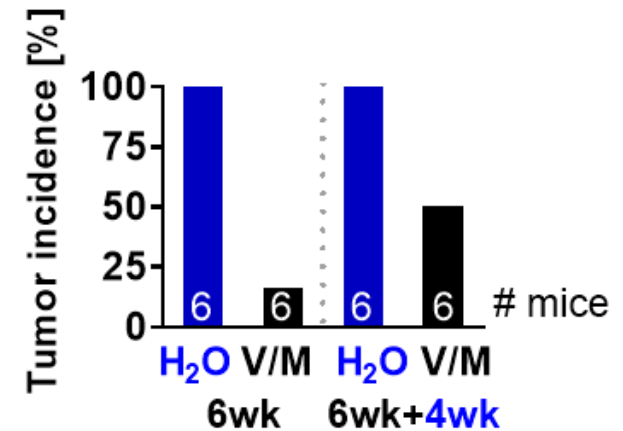
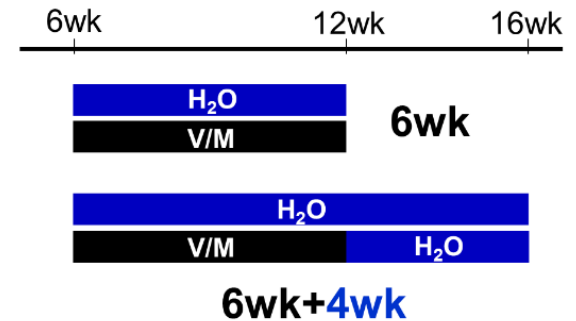
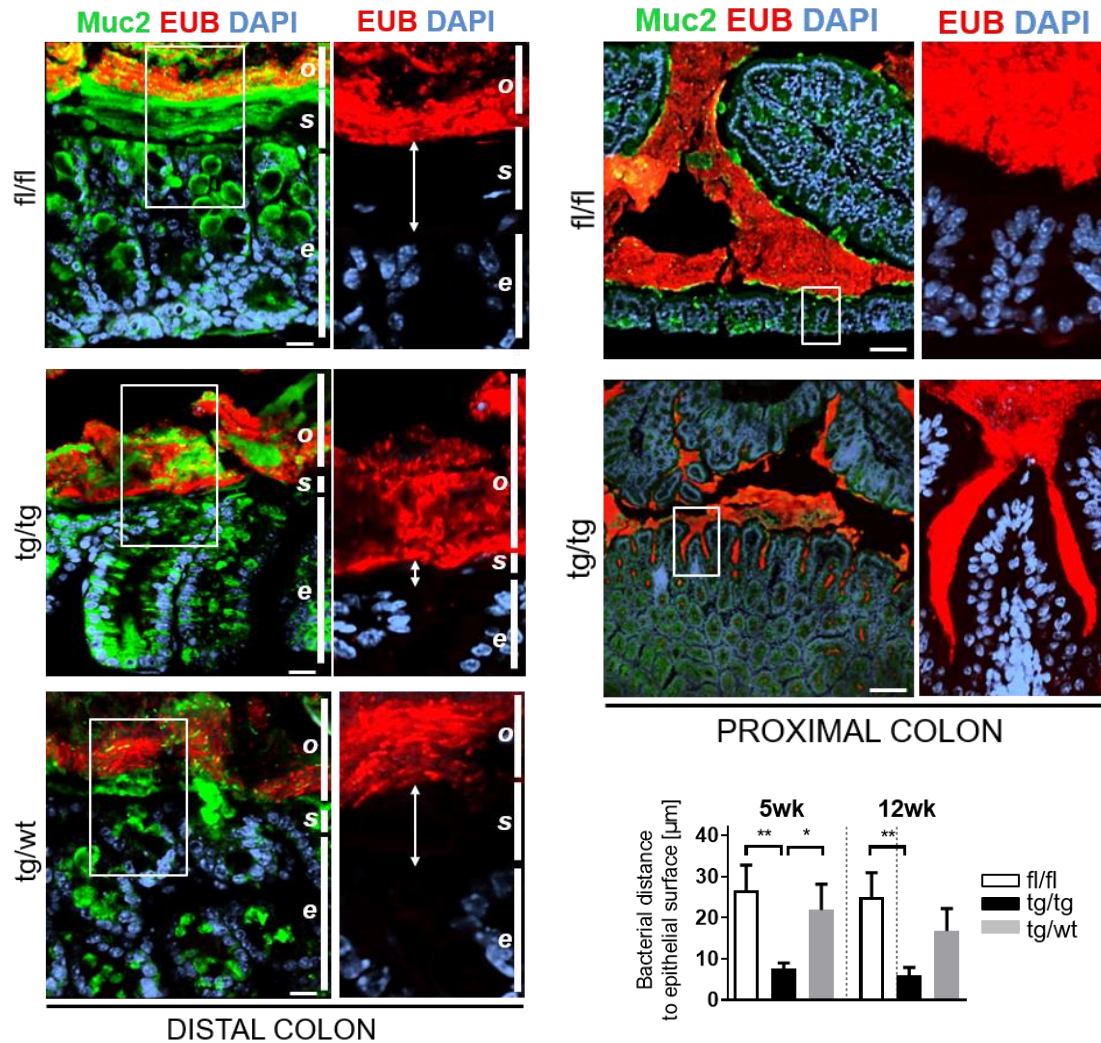
Activated ATF6 triggers spontaneous colonic tumors



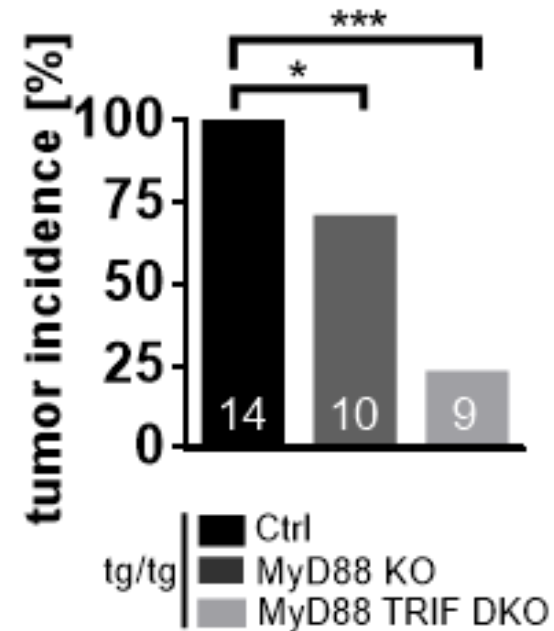
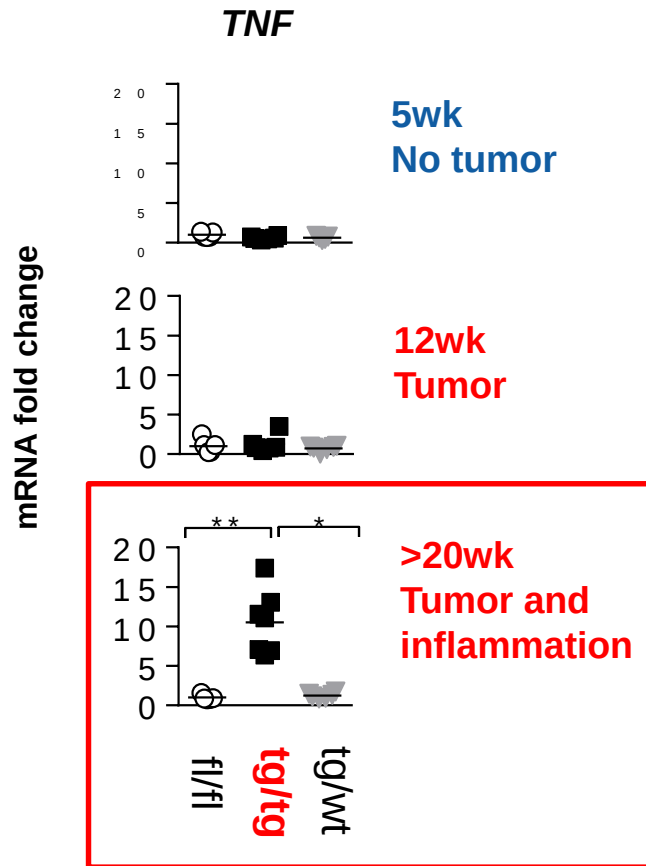
Microbiota changes independent of inflammation



Bacteria penetrate the mucus barrier

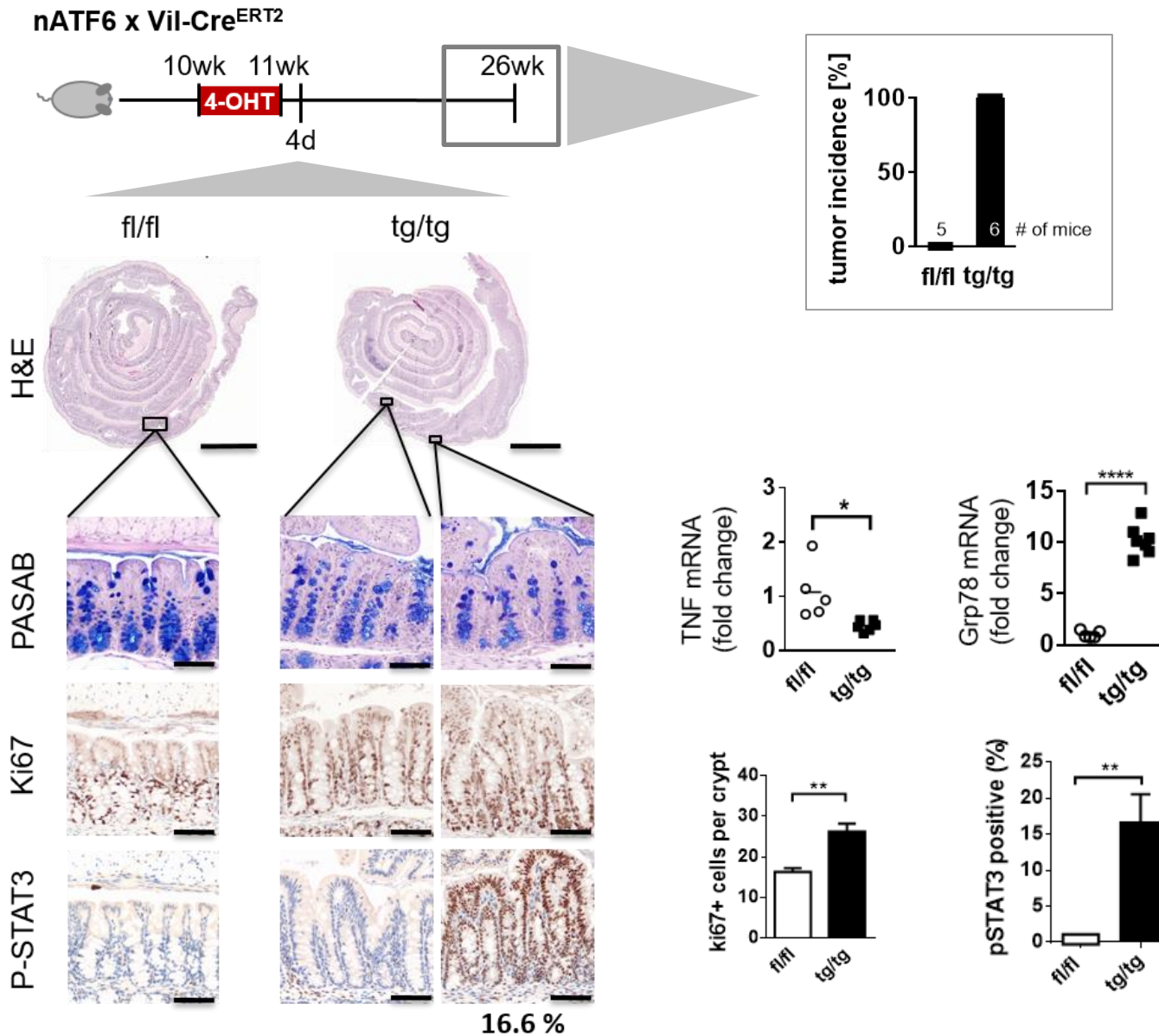


TLR related TRIF signaling triggers tumors

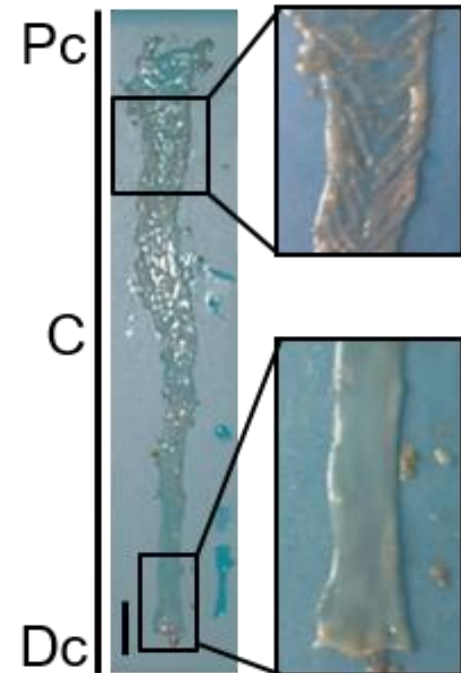
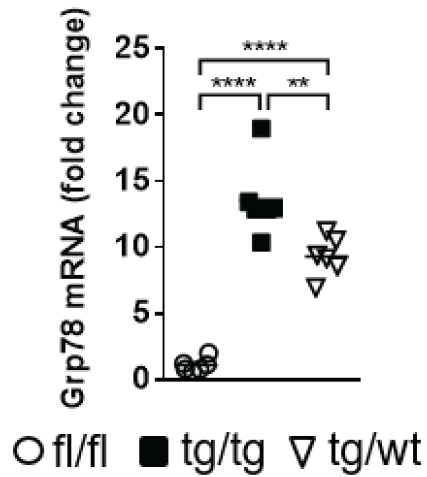
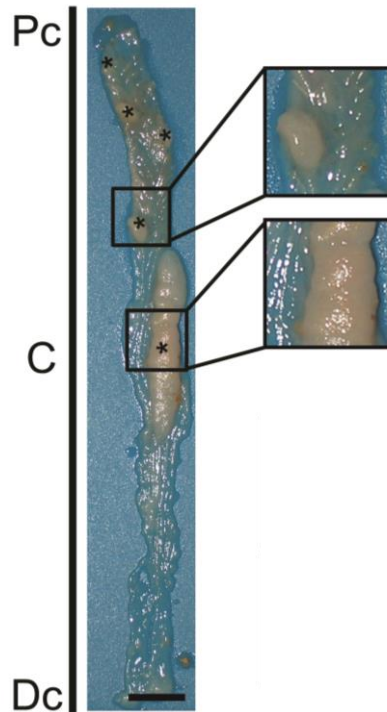
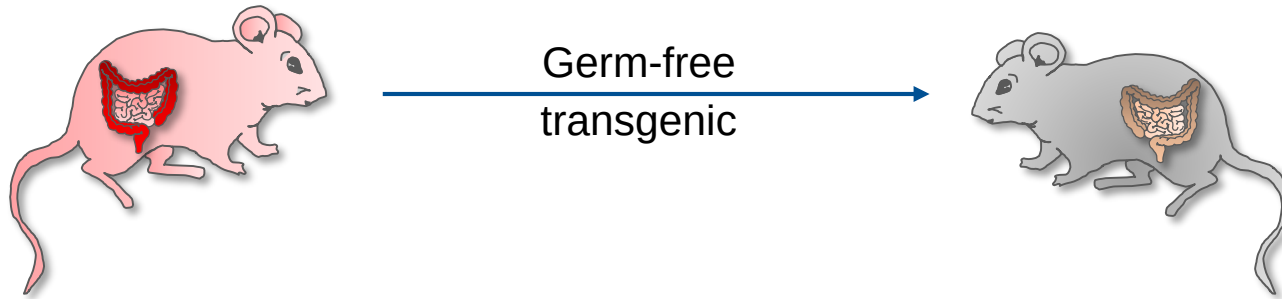


... but independent of inflammation

Focal STAT3 activation at very early stages

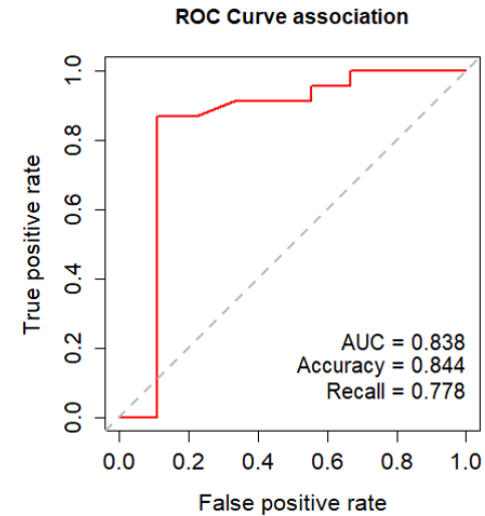
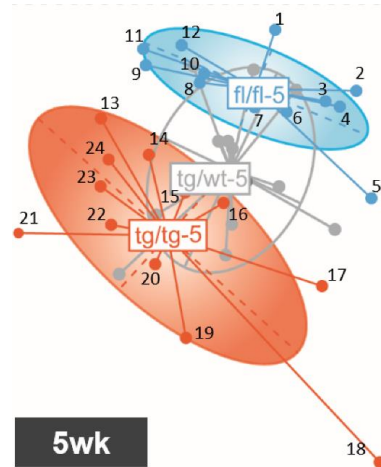


Germ-free mice are protected despite cell stress

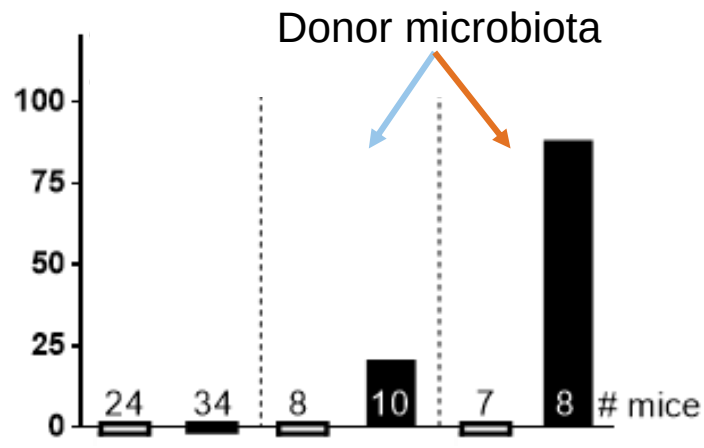


Transmissive tumor formation

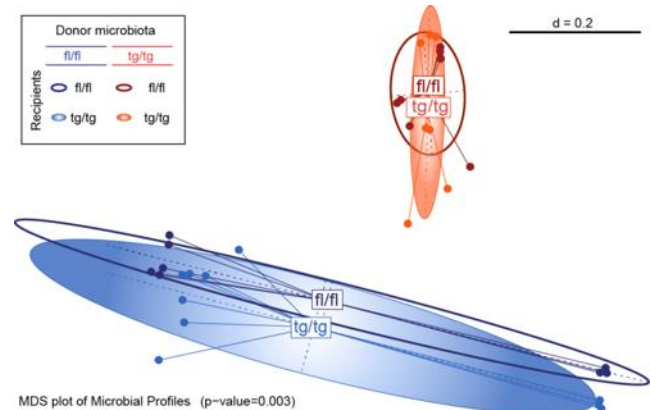
Microbiota before tumor (5w)



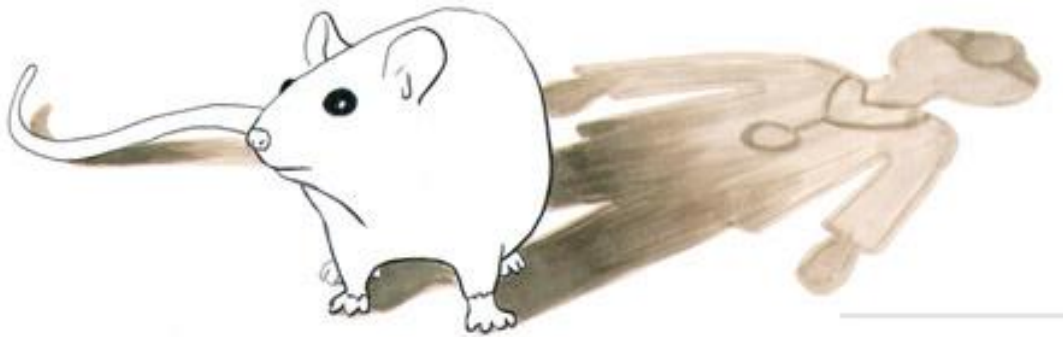
Tumor incidence (%)



Control (fl/fl) recipient
ATF6 (tg/tg) recipient



Transfer of phenotypes via microbiota transplantation



from **mouse** to mouse or
mouse to **human**

Mouse to mouse in IBD and colorectal cancer models

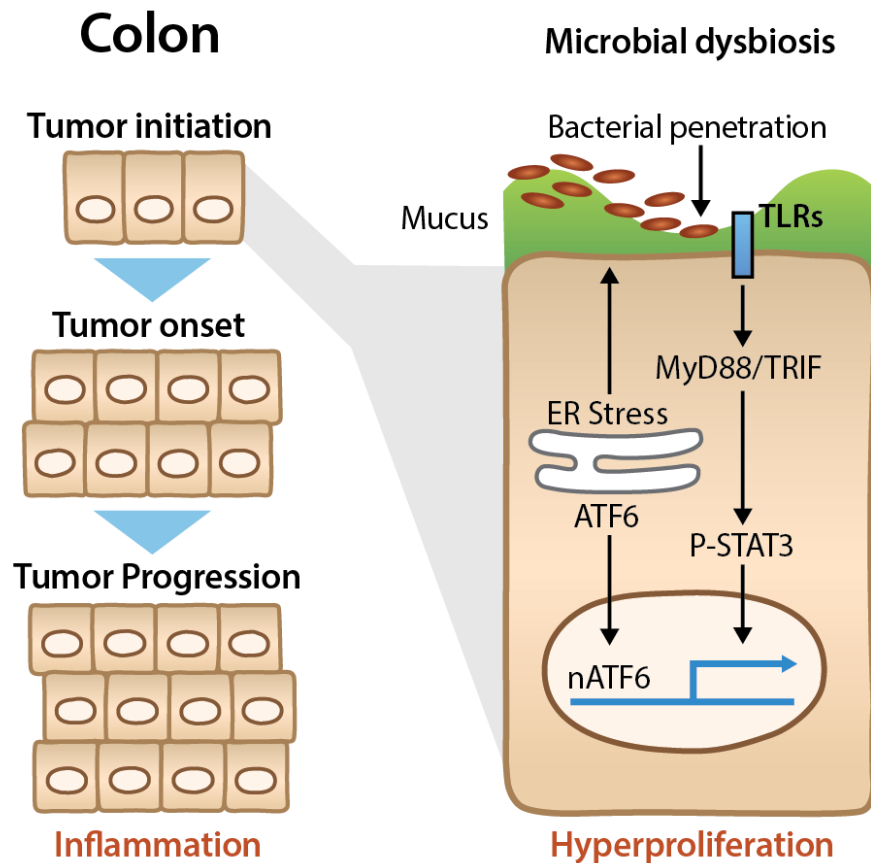
- ✓ Schaubeck, ..., Haller 2016 Gut
- ✓ Coleman, ..., Haller 2018 Gastroenterology

Human to mouse in IBD and obesity models

- ✓ **Metwaly, ..., Haller (unpublished)**
- **Schueppel, ..., Haller (unpublished)**



Gnotobiotic facility, ZIEL, TUM



- ATF6 is relevant for 10% of CRC patients
- ATF6 activation is conditioning the tumor niche
- Microbial environment triggers tumor formation independent of tissue inflammation
- Community vs. selective function of single microbes unclear

... and all depends on the people!

Cleveland University

Fabio Cominelli

U Alberta

Richard Fedorak

Chapel Hill

R. Balfour Sartor

Barcelona

Julian Panes
Azucena Salas

Paris

Matthieu Allez

RWTH Aachen

Thomas Clavel

University of Luxembourg

Paul Wilmes, Emanuel Berger

DKFZ

Mathias Heikenwälder



Munich

Martin Klingenspor
Klaus-Peter Janssen
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Nina Heppner,

Nico Gebhardt, Silvia Pitariu,
Simone Daxauer, Felicitas Firlus

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