Helicobacter pylori persistence and immunomodulation

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*Helicobacter pylori* resides in the human stomach, where it can cause gastritis, peptic ulcer disease and gastric cancer.

Carriers with clinically overt disease (10-20% of infected population)

*H. pylori* on gastric epithelial cells
*Helicobacter pylori* resides in the human stomach, where it can cause gastritis, peptic ulcer disease and gastric cancer... or remain asymptomatic

Carriers with clinically overt disease (10-20% of infected population)

Asymptomatic carriers (>80% of infected population)
Helicobacter pylori resides in the human stomach, where it can cause gastritis and peptic ulcer disease... or remain asymptomatic.

Carriers with clinically overt disease (10-20% of infected population) modeled by adult infection

Asymptomatic carriers (>80% of infected population) modeled by neonatal infection of mice

in humans: Harris et al., Gastroenterology 2008
Robinson et al., Gut 2008
in mice: Arnold et al., Gastroenterology 2011
The *H. pylori* virulence/persistence factors VacA and GGT are required for DC tolerization, regulatory T-cell differentiation and persistence.
VacA promotes the generation of peripherally induced pTregs in the gastric lamina propria and their enrichment in the lung.
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VacA interacts with various myeloid cells in the gastric LP and promotes a tolerogenic transcriptional program

qRT-PCR of CX3CR1+ macrophages after VacA exposure

qRT-PCR of CX3CR1+ macrophages after live Hp exposure

Altobelli et al. MBio 2019
VacA interacts with various myeloid cells in the gastric LP and promotes a tolerogenic transcriptional program.

qRT-PCR of CX3CR1+ macrophages after VacA exposure

qRT-PCR of CX3CR1+ macrophages after live Hp exposure
CD11b+ DCs and monocytes and macrophages, but not CD103+ DCs, encounter *H. pylori* in the infected gastric mucosa.

Arnold et al. Cell Reports, 2017
H. pylori is inversely associated with allergies and chronic inflammatory diseases

Chen & Blaser, 2007; Reibman et al., 2008; Chen & Blaser, 2008; Amberbir et al., 2011, 2014, Genta et al, 2015
Neonatally infected mice are protected against clinical parameters of ovalbumin-induced asthma/allergic airway disease

Neonatally infected mice, but not mice infected as adults, have elevated frequencies of pTregs in their lungs.
VacA is required for infection-induced asthma protection and induction of allergy-suppressing Tregs
VacA confers asthma protection when administered in purified form, beginning in early life.
Helicobacter pylori colonization confers protection against allergic asthma (and IBD) through its immunomodulator VacA

Arnold et al., JCI 2011, Oertli et al., JCI 2012, PNAS 2013
Engler et al., PNAS 2014, Infl. Bowel Diseases 2015
Meta-analyses: Castaño-Rodríguez et al. Gut 2017,
Trans-maternal *Helicobacter pylori* exposure *in utero* and/or during lactation has protective effects on offspring

Andreas Kyburz

Kyburz et al. JACI 2018
*Helicobacter pylori* VacA has protective effects on offspring exposed during lactation

Kyburz et al. JACI 2018
Antibiotic exposure during the second week of life has the opposite effect on pTreg frequencies (and allergic asthma).

Colonic Tregs:

with T. Borbet and M. Blaser
In the absence of BATF3-dependent CD103\(^+\) DCs, there is less Th1 recruitment to infected tissues ⇒ infection control is impaired.
BATF3-dependent DCs are required for pTreg recruitment to the *H. pylori*-infected gastric mucosa.
BATF3-dependent DCs promote effector and regulatory T-cell recruitment to infected tissues through two distinct mechanisms.
Conclusions

-VacA is a persistence determinant that interacts with myeloid cells in the gastric LP and skews T-cell responses towards Tregs

-direct and trans-maternal exposure to *H. pylori* (or VacA) has trans-generational protective effects in models of allergen-induced asthma

-*H. pylori* induces pTregs that express Tbet and RORγt and follow a chemokine gradient to infected tissues

-CD103+ DCs have a non-redundant role in T-cell recruitment (effector T-cells and Tregs, to infected and tumor tissues and distant sites)

-*H. pylori* interacts with eosinophils in the gastric lamina propria
Chronic *Helicobacter*-induced inflammation results in preneoplastic gastric pathology

PCNA  BrdU  Overlay

control  infected

Epithelial hyperplasia

Intestinal metaplasia
*H. pylori* induces DNA double strand breaks in the nuclear genome of its host cells.

Toller et al., *PNAS* 2011
Screening for *H. pylori* factors involved in DNA double strand break induction reveals a role for the type IV secretion system (T4SS)

Hartung et al., *Cell Reports* 2015
H. pylori-induced DNA DSBs require transcription, a functional type IV secretion system and NF-κB signaling
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