Gut Microbiota and the Development of the Human Immune System

Ger Rijkers
The classic, co-evolutionary, immune system-boosting tango between mammals and the beneficial bacteria that inhabit their gut
Surrounded by a world of micro-organisms and inhabited
T Lymphocyte Development

- Starts in week 7
- Rearrangment of T cell receptors (αβ TCR and γδ TCR)
- Positive selection on MHC
- Negative selection for self

Note: T cell repertoire development antigen independent
B-lymphocyte development

Note: B cell repertoire development antigen independent
When children are born, they emerge from the relatively sterile environment of the uterus into a world teeming with bacteria . . .
T Lymphocytes: naïve vs memory/effector

Neonate

Adult

CD45RA (naïve)

CD45RO (memory)

CD45RO (memory)
CD4⁺ T-lymphocyte subsets

Underdeveloped at birth

Overactive in autoimmune diseases

Underdeveloped in allergic and autoimmune diseases

Overactive in allergy

- Th0
- Th1
- Th2
- Tbet
- FOXP3
- GATA3
- RORγT
- IL-17
- IL-22
- TNF-α

Macropl Regulation of cellular immunity
Viruses Intracellular bacteria
Bacteria Worms (helminths) Allergens

Humoral immunity
Interactions of Gut Microbiota with the Host Immune System

Dendritic cell: Bridging innate and acquired immunity

- Co-stimulatory molecules CD80, CD86, etc
- Cytokine production

**TLR**

**PAMP**

**Myd88**

**NFκB**

**endocytosis promoting receptor**

**T-lymphocyte**
Toll-like receptors recognize molecular patterns on micro-organisms
Neonatal tolerance

Peptidoglycan

TLR2

CXCL8

IL-8

Data Edward Nieuwenhuis (in prep.)
Immunosuppressive CD71+ erythroid cells compromise neonatal host defence against infection

Shokrollah Elahi1, James M. Erten1, Jeremy Burn1, Beverly S. Strong2, Joseph McCusker1, Vandana Chaturvedi3,4,5 & Sing Sing Way1

...susceptible to infection... 

...CD71+ cell-mediated protection against abnormal immune cell activation in the intestine, where colonization with commensal microorganisms occurs swiftly after parturition10,11. Conversely, circumventing such colonization by using antimicrobials or gnotobiotic germ-free mice overrides these protective benefits. Thus, CD71+ cells quench the excessive inflammation induced by abrupt colonization with commensal microorganisms after parturition. This finding challenges the idea that the susceptibility of neonates to infection reflects immune-cell-intrinsic defects and instead highlights processes that are developmentally more essential and inadvertently mitigate innate immune protection. We anticipate that these results will spark renewed investigation into the need for immunosuppression in neonates, as well as improved strategies for augmenting host defence in this vulnerable population.

...are highly susceptible to disseminating... 

Numerous infections have direct respon...
Immunosuppressive CD71+ erythroid cells compromise neonatal host defence against infection

Shokrollah Elahi¹, James M. Ertelt¹, Jeremy M. Kinder¹, Tony T. Jiang¹, Xuzhe Zhang¹, Lijun Xin¹, Vandana Chaturvedi¹, Beverly S. Strong², Joseph E. Qualls¹, Kris A. Steinbrecher³, Theodosia A. Kalfa⁴, Aimen F. Shaaban² & Sing Sing Way¹
CD4⁺ T-lymphocyte subsets

Dendritic cell → Th0 → Th1 → Tbet → IFN-γ, TNF-α, IL-2

Dendritic cell → Th0 → Th17 → RORγT → IL-17, IL-22, TNF-α

Dendritic cell → Th0 → Th2 → GATA3 → IL-4, IL-5, IL-13

Treg → FOXP3 → IL-10

Macrophage activation
Regulation of cellular immunity

Balance

Regulation of humoral immunity

Viruses
Intracellular bacteria

Bacteria
Worms (helminths)
Allergens
57 species common to >90% of individuals
B. fragilis PSA controls CD4 T lymphocyte development in GF mice

Mazmanian et al., Cell, Vol. 122, 107–118, July 15, 2005,
A microbial symbiosis factor prevents intestinal inflammatory disease
BACTERIAL BALANCE

H. hepaticus

B. fragilis

intestinal lumen

T_{H}^{17} cells

IL-17, IL-23 & TNF

pro-inflammation signals

PSA

NO INFLAMMATION!

CD4+ cell

T_{H}^{1 cell}

T_{R}es cell

Colitis
Gut Microbiota and the Development of the Human Immune System
Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation

Nicholas Arpaia\textsuperscript{1,2}, Clarissa Campbell\textsuperscript{1,2}, Xiying Fan\textsuperscript{1,2}, Stanislav Dikiy\textsuperscript{1,2}, Joris van der Veeken\textsuperscript{1,2}, Paul deRoos\textsuperscript{1,2}, Hui Liu\textsuperscript{3}, Justin R. Cross\textsuperscript{3}, Klaus Pfeffer\textsuperscript{4}, Paul J. Coffer\textsuperscript{1,2,5} & Alexander Y. Rudensky\textsuperscript{1,2}

Wel darmbacteriën, geen pathogenen
4 antibiotica:
geen levende bacteriën
Germ free:
geen bacteriën
Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation

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Wel darmbacteriën, geen pathogenen
4 antibiotica:
geen levende bacteriën
Germ free:
geen bacteriën
Short Chain Fatty Acids

Acetic acid (acetate)

Propionic acid (propionate)

Butyric acid (butyrate)
Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation

Nicholas Arpaia¹,², Clarissa Campbell¹,², Xiyong Fan¹,², Stanislav Dikiy¹,², Joris van der Veeken¹,², Paul deRoos¹,², Hui Liu³, Justin R. Cross⁴, Klaus Pfeffer⁴, Paul J. Coffer¹,²,⁵ & Alexander Y. Rudensky¹,²
Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells

Yukihiro Furusawa1,2,*, Yuuki Obata1,2,*, Shinji Fukuda1,4,*, Takahiro A. Endo1, Gaku Nakato1, Daisuke Takahashi1, Yumiko Nakanishi5, Chikako Uetake1, Keiko Kato1,5, Tamotsu Kato1, Masumi Takahashi1, Noriko N. Fukuda4, Shinnosuke Murakami4, Eiji Miyauchi1, Shingo Hino6, Koji Atarashi7, Satoshi Onawa1, Yumiko Fujimura2, Trevor Lockett8, Julie M. Clarke8, David L. Topping9, Masaru Tomita4, Shohei Hori1, Osamu Ohara1, Tatsuya Morita6, Haruhiko Koseki1,5, Jun Kikuchi5,9, Kenya Honda1,10, Koji Hase1,2,7,9 & Hiroshi Ohno1,5

![Graphs showing the differentiation of colonic regulatory T cells with untreated, acetate, propionate, and butyrate treatments.](image)
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Supplementary Figure 22 | A schematic diagram of epigenetic modifications by commensal microbial fermentation product.

*Clostridiales* abundantly produce butyrate, which promotes histone H3 lysine acetylation in *Foxp3* gene locus of CD4+ T cells, and eventually facilitates induction of Treg cells. APC: antigen-presenting cells.

doi:10.1038/nature12721
Extrinsic and Intrinsic Factors contribute to Development of Allergic diseases

- Environment
- Genetic
- Mucosa, Epithelia
- Nervous system
- Immune system
- Gut microbiota
- Maternal-Fetal Interaction

Clinical expression of disease

M. Kalliomäki, J-M Antoine, U Herz, GT Rijkers
Box 5 | Unresolved areas of translational investigation

Although there has been much learned about the pathogenesis of type 1 diabetes (T1D) as a result of preclinical and clinical studies, several key questions have arisen and remain unanswered. Some of these are addressed here.

What are the initiating factors?
- Are viruses involved? Are these unique or common?
- Are any of these factors intrinsic to β-cells in T1D patients?
- Which antigens are presented, and does this change over time or in different patients?
- How does the microbiome affect the induction or progression of autoimmunity?
- How are innate responses involved?
- What is the role of epigenetic changes in the penetrance of disease?

How does the immune repertoire differ in patients who will develop T1D?
- What is the antigen specificity of pathogenic T cells, and how can these cells be identified?
- How much of the disease heterogeneity stems from stochastic variation in immune development versus exposure to natural pathogens versus normal responses to one’s environment?
- Why does it take so long to destroy all of the β-cells?
- Are there unusual features of autoreactive T cell development pathways?
- How do immune response and other genes affect disease in general or the diabetogenic potential of T cells specifically?
- What is the role of cell-intrinsic regulatory mechanisms?
- What are the roles of thymus-derived and peripherally induced regulatory T cells?
Guts, Germs, and Meals: The Origin of Type 1 Diabetes

H. Beyan · L. Wen · R. D. Leslie

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Abstract Type 1 diabetes mellitus (T1DM) is a non-genetically determined factor including environmental factors. The nature of these environmental factors is unclear but they are important to identify since they are amenable to therapy. Recently, the gut microbiota of microorganisms inhabiting the gut, as well as maternal infections, has been implicated in T1DM pathogenesis. Since dietary changes can reshape this complex gut community, its co-evolution could have been altered by changes to our diet, agriculture, personal hygiene, and antibiotic usage, which coincide with genetic associations [1, 2] are reflected in the increased risk for T1DM in monozygotic co-twins and non-diabetic siblings with both HLA-DR3/4 and autoantibodies [3-6]. These genetic associations, including HLA alleles...
1. Sex-biased autoimmunity in the NOD mouse depends on the microbiome.
Gavage of female NOD pups with male NOD-derived intestinal microbiome results in T1D protection, reduced insulitis severity and insulin auto-antibody titer by an androgen-dependent mechanism. Female NOD
Welcome to the Microgenderome

Gender, microbes, and disease. Male puberty (in mice; not shown) leads to changes in the gut microbiota that reinforce testosterone production, which is protective against the development of T and B cell functions linked to autoimmune disease. In mice, the protective properties of the male-associated microbiota can be transferred to younger females and confer...
Gut Bacteria May Be Implicated in Rheumatoid Arthritis

BY BETH SKWARECKI, SCIENCENOW 11.05.13 10:30 AM
Expansion of intestinal *Prevotella copri* correlates with enhanced susceptibility to arthritis

Jose U Scher\(^1\), Andrew Sczesnak\(^2,3\), Randy S Longman\(^2,4\), Nicola Segata\(^5,6\), Carles Ubeda\(^7,8\), Craig Bielski\(^6\), Tim Rostron\(^9\), Vincenzo Cerundolo\(^9\), Eric G Pamer\(^7\), Steven B Abramson\(^1\), Curtis Huttenhower\(^6\), Dan R Littman\(^2,10\)*

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>n</th>
<th>Duration (mo)</th>
</tr>
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<tbody>
<tr>
<td>NORA</td>
<td>New Onset Rheumatoid Arthritis</td>
<td>44</td>
<td>5.4</td>
</tr>
<tr>
<td>CRA</td>
<td>Chronic, treated Rheumatoid Arthritis</td>
<td>26</td>
<td>72.3</td>
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<tr>
<td>PsA</td>
<td>Psoriatic Arthritis</td>
<td>16</td>
<td>0.8</td>
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<tr>
<td>HLT</td>
<td>Healthy</td>
<td>28</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Scher et al. eLife 2013;2:e01202. DOI: 10.7554/eLife.01202
Expansion of intestinal *Prevotella copri* correlates with enhanced susceptibility to arthritis

Jose U Scher¹†, Andrew Sczesnak²,³†, Randy S Longman²,⁴†, Nicola Segata⁵,⁶, Carles Ubeda⁷,⁸, Craig Bielski⁹, Tim Rostron⁹, Vincenzo Cerundolo⁹, Eric G Pamer⁷, Steven B Abramson¹, Curtis Huttenhower⁶, Dan R Littman²,¹⁰∗
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Scher et al. eLife 2013;2:e01202. DOI: 10.7554/eLife.01202
Relative abundance of *P. copri* in NORA inversely correlates with presence of shared-epitope risk alleles

Certain alleles within the human leukocyte-antigen (HLA) Class II locus confer higher risk of disease, in particular those belonging to DRB1 (i.e., ‘shared epitope’ alleles or SE) (du Montcel *et al.*, 2005; Gregersen *et al.*, 1987). To determine whether a higher abundance of *P. copri* is associated with the host genotype, we carried out HLA sequencing on DNA from all participants in our study (Supplementary file 1E). Consistent with recently published mouse data (Gomez *et al.*, 2012), the presence of SE

![Diagram](image)

**Figure 4.** Metabolic pathway representation in the microbiome of healthy and NORA subjects. HUMAnN

Scher *et al.* eLife 2013;2:e01202. DOI: 10.7554/eLife.01202
Microbiota-mediated colonization resistance against intestinal pathogens

Charlie G. Buffie and Eric G. Pamer

Manipulation and reconstitution of the microbiota

Colonization resistance that is conferred by endogenous commensal bacteria can be therapeutically exploited, but the use of adoptively transferring commensal bacteria to a host associated with adoptive transfer of intestinal species related to C. difficile aids in the cure of C. difficile. 33 taxonomically from...