

# Journal Club

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15/8/2016

# Paper 1

Immunity  
Article

## Microbiota-Dependent Activation of an Autoreactive T Cell Receptor Provokes Autoimmunity in an Immunologically Privileged Site

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# Relevance

Balancing act of host and commensal bacteria between:

**profit** (metabolism, protection from pathogens, IS development) vs. **danger** (inflammatory and autoimmune disease)

Where and how do T cells first become activated to a self antigen that resides behind blood-tissue barrier?

→ T cells receive an activation signal in the gut that is independent of the endogenous retinal antigen

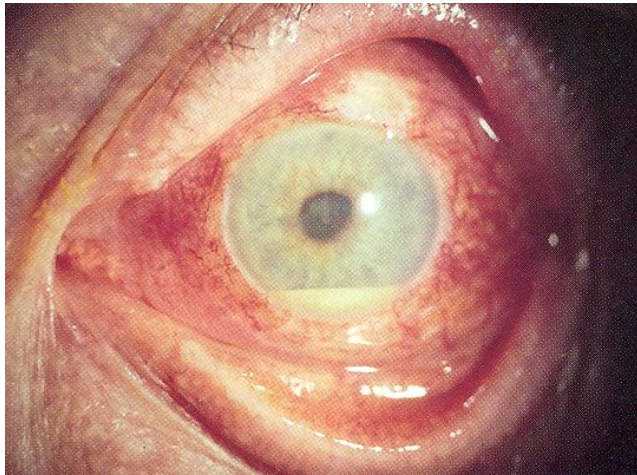
# Background

- Th17 cells induced by microbial components
- Th17 as important T cell effectors in autoimmune disease

## Recent studies have shown:

- Contribution of gut commensal microbiota for inflammatory and autoimmune disease in various animal models

## Uveitis:



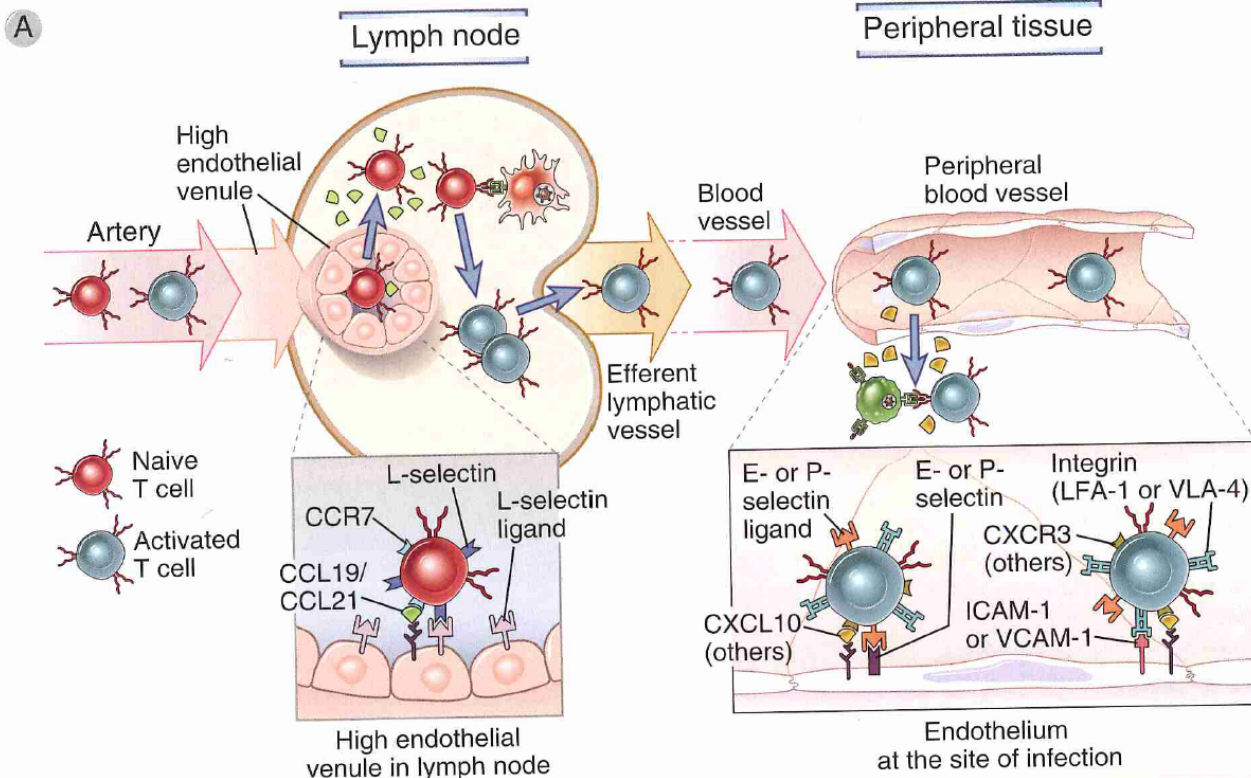
- Autoimmune disease and major cause of blindness
- Th17 driven
- Immune response to unique retinal proteins involved in visual function such as retinal arrestin and interphotoreceptor retinoid binding protein (IRBP)
- Animal models:
- Immunization with retinal protein in healthy WT mice
- Transfer of uveitogenic T cells into healthy WT mice
- **spontaneous uveitis: transgenic mice** with enhanced frequency of retina-specific T cells which seem to amplify the naturally low penetrance of uveitis to a frequency that can be studied in the lab

# Background

## Open question:

Retinal antigen (IRBP) hidden in immunoprivileged site in the eye

To cross blood-tissue and induce uveitis, autoreactive antigen-specific T cells must be first activated



**Immune system**

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**Retinal antigen  
(protected)**

**Eye: Immune  
privileged site**

# References

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## **2) Commensal bacteria trigger autoimmunity**

- Garrett, W. S., et al. (2010). "Enterobacteriaceae act in concert with the gut microbiota to induce spontaneous and maternally transmitted colitis." Cell Host Microbe **8**(3): 292-300.

- Berer, K., et al. (2011). "Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination." Nature **479**(7374): 538-541.

## **3) SFB induce Th17 cell response → autoimmunity but Th17 are SFB specific:**

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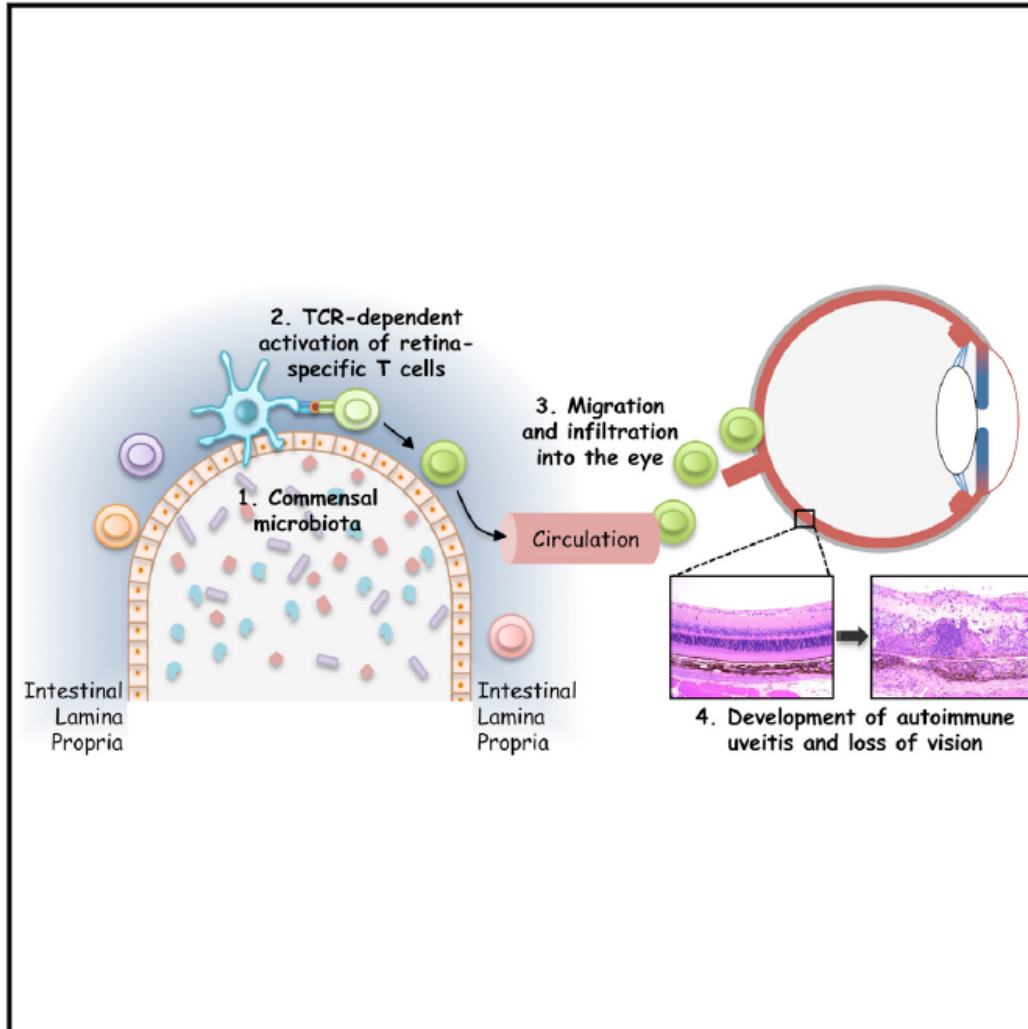
- Yang, Y., et al. (2014). "Focused specificity of intestinal TH17 cells towards commensal bacterial antigens." Nature **510**(7503): 152-156.

## **4) Mouse model of spontaneous uveitis:**

- Horai, R., et al. (2013). "Breakdown of immune privilege and spontaneous autoimmunity in mice expressing a transgenic T cell receptor specific for a retinal autoantigen." J Autoimmun **44**: 21-33.

# Major Finding

## Graphical Abstract



- Retina specific T cells receive an TCR-dependent activation signal in the gut that is independent of the endogenous retinal antigen
- Thereafter migration and infiltration of activated autoaggressive T cells into the eye is observed
- Followed by the development of autoimmune uveitis

# Paper 2

Immunity  
**Article**

## **Lymphoid-Tissue-Resident Commensal Bacteria Promote Members of the IL-10 Cytokine Family to Establish Mutualism**

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# Relevance

Balancing act of host and commensal bacteria between:

**profit** (metabolism, protection from pathogens, IS development) vs. **danger** (inflammatory and autoimmune disease)

→ Common concept: Commensals in lumen are separated from intestinal lymphoid tissues to prevent inflammation

Still: There are commensals found in intestinal lymphoid tissue → what is their functional relevance?!

# Background

- Commensal bacteria: nutrient metabolism, pathogen infection, IS development & maturation
- Healthy state: commensals in lumen, physically separated from IS in LP and intestinal lymphoid tissues (epithelial cells, tight-junction proteins, anti-microbial peptides, mucus, IgA)
- Prevention of pathologic inflammation
- **Recent findings:** unique subset of commensal can colonize intestinal lymphoid tissues of healthy mammals (PPs, mLNs, isolated lymphoid follicles)
- Found associated with CD11c+ DCs
- IL-22 and ILC3 important in preventing systemic dissemination of one LRC *Alcaligenes* and systemic inflammation
- Suggest: innate immune pathway maintain anatomical containment between LRCs and systemic IS
- **Open question:** mechanisms and functional significance

# References

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- Hooper, L. V. and A. J. Macpherson (2010). "Immune adaptations that maintain homeostasis with the intestinal microbiota." Nat Rev Immunol **10**(3): 159-169.

## **2) Commensal bacteria influence immune cells indirectly:**

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## **3) Bacteria can be found in gut-associated lymphoid tissues:**

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## **4) Commensal in intestinal lymphoid tissues, IL-22 by ILC3 limit their systemic colonization:**

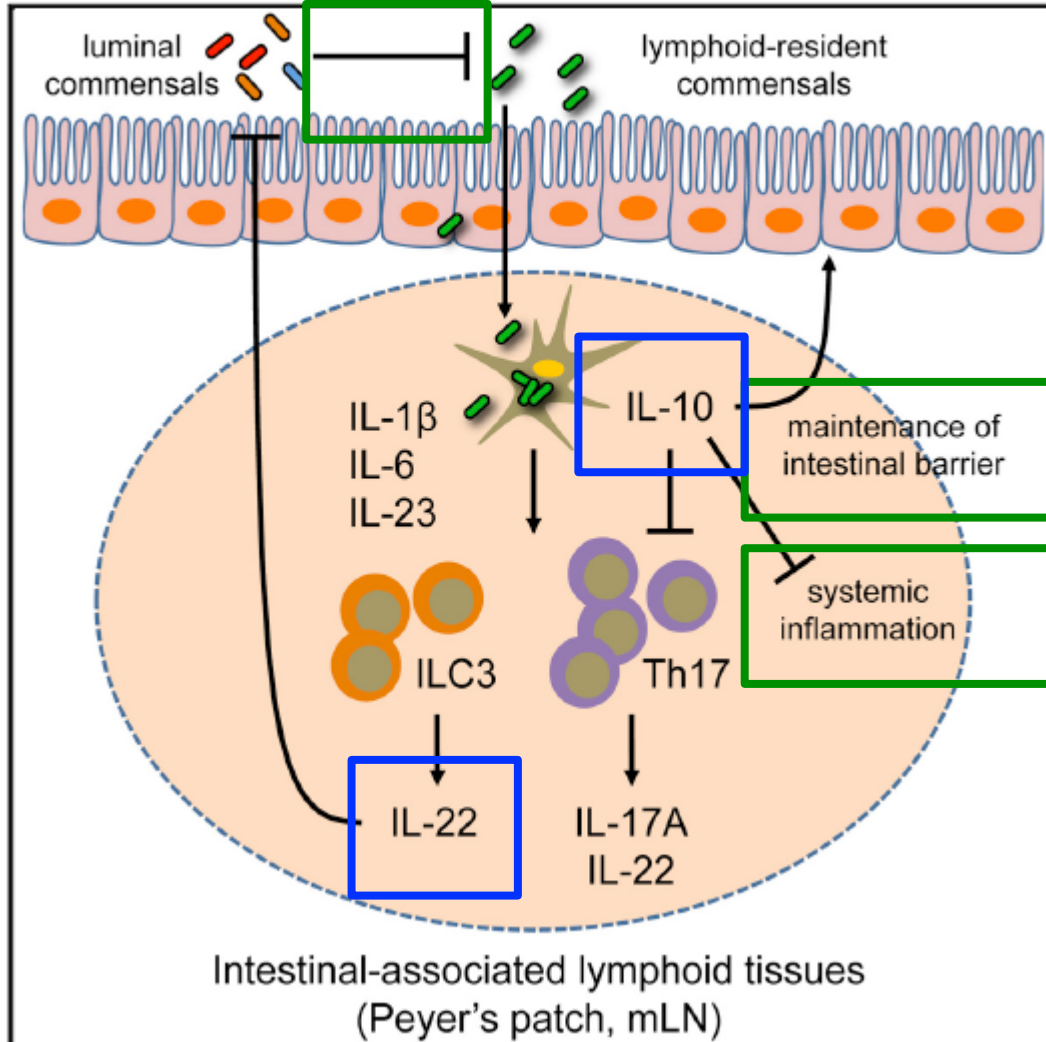
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## **5) Recognition of microbial signal is critical for maintenance of intestinal barrier**

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# Major Finding

## Graphical Abstract



- Commensal bacteria (lymphoid-tissue-resident commensal bacteria = LRCs) colonize CD11c<sup>+</sup> and modulate their cytokine production
- IL-10 and ILC3-derived IL-22
- IL-22 enhanced LRC colonization
- IL-10: limited Th17 cell response
- LRC protected mice in a IL-10 dependent manner from intestinal damage