Journal Club

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Article

Cell

Regulatory T Cell Specificity Directs Tolerance versus Allergy against Aeroantigens in Humans

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Relevance & References

- Regulatory T cells control aberrant Th2 responses and type 1 hypersensitivity
  - IPEX syndrome (Barzaghi, Front Immunol, 2012)
  - mice lacking peripheral Tregs (CNS1-deficient, Josefowicz, Nature, 2012)
- Allergic patients develop disease only against limited nr. of allergens - Tolerance against most proteins maintained
- Antigen specificity of Treg?
  - mostly autoantigens (Hsieh, Immunity, 2004; Kieback, Immunity, 2016)
  - exogenous antigens both before and after exposure to them (Suffia, JEM, 2006; Zhao, JEM, 2011; Moon, PNAS, 2011; Shafiani, Immunity, 2013)
  - commensal antigens (Geuking, Immunity, 2011; Lathrop, Nature, 2011; Cebula, Nature 2013)

Role of antigen-specific Treg responses for the prevention of allergy remained elusive

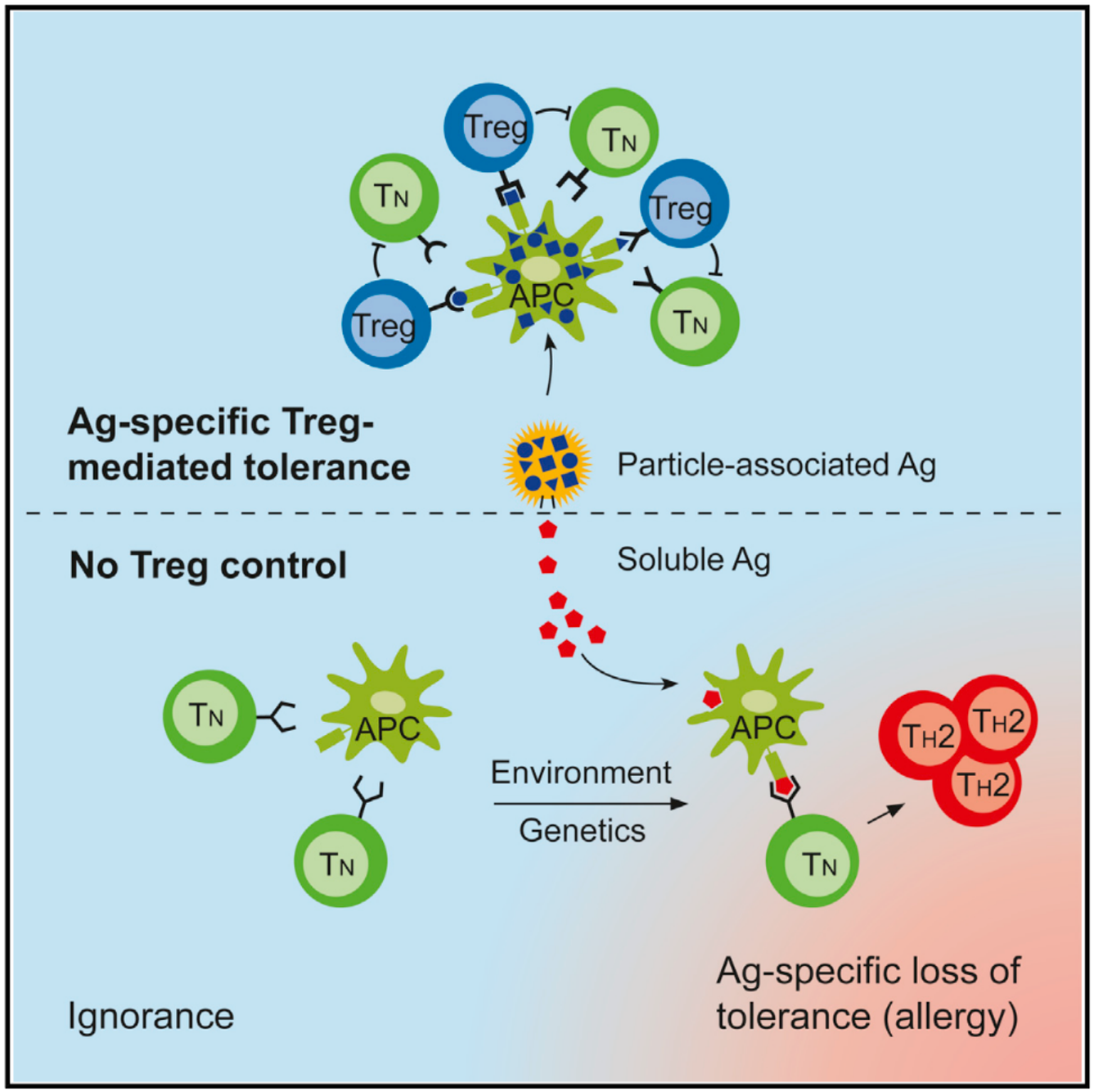
Findings

- Airborne antigens (allergens) induce antigen-specific Treg response (shown for PMBCs)
- Allergic patients show NO defect in Treg response specific to intact antigens or lysates but still aberrant antigen-specific Th2 cell activation
- In aqueous solutions, intact allergic particles (e.g. Birch pollen) dissociate into
  - soluble proteins that don't drive Treg differentiation but induce Th2 responses in allergic patients
  - proteins that remain particle-associated and readily induce Tregs able to prevent Th2 activation

Th2 cell-repressing Tregs are generated against particulate airborne antigens in both healthy and allergic people while soluble proteins poorly induce Tregs but rather Th2 cells that predispose to the development of allergies.

Summary

- Airborne allergens induce robust antigen-specific Treg responses in healthy individuals and allergic patients.
- Tregs fail to control aberrant Th2 responses in allergic patients because they are directed against particulate antigens while soluble antigens provoke the disease-inducing Th2 response.



Resource

Cell

Linking the Human Gut Microbiome to Inflammatory Cytokine Production Capacity

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Relevance & References

- Many inflammatory and autoimmune diseases associated to dysbiosis (**IBD**: Frank, PNAS, 2007; Gevers, Cell H&M, 2014; **Allergy**: Abrahamsson, Clin Exp Allergy, 2013; **Rheumatoid Arthritis**: Zhang, Nat Med, 2015, **Type I diabetes**: Paun, J Autoimmun, 2016; and many more)
- Inflammatory diseases linked to aberrant cytokine responses, evidenced by e.g. infliximab treatment (anti-TNF antibody) for IBD, anti-IL-23 for psoriasis etc.
- How is dysbiosis, or generally microbiome composition linked to exaggerated cytokine responses?

The Human Functional Genomics Project aimed to link differences in cytokine responses to

- host genetics (Li, Cell, 2016)
- host and environmental factors (ter Horst, Cell, 2016)
- microbiome (this paper)

Findings

- In healthy individuals, up to 10% of inter-individual variation in cytokine responses can be attributed to microbiome (composition but also function, i.e. presence of metabolic pathways) (comp. to 25-50% explained by host genetics!)
- Correlation finding: *Coprococcus comes* stimulates acute phase response, e.g. alpha-1-antitrypsin, IL-1β
- Validated finding 1: Tryptophol, product of microbial Tryptophan katabolism, inhibits IFN-γ secretion *in vitro*
- Validated finding 2: Microbiota influences levels of palmitoleic acid which inhibits IL-1β, IL-6 and TNF levels *in vitro*

Overall, the paper links the microbiome to cytokine responses mostly on a correlative basis.

While the approach probably reveals several false positives (FDR=0.2) and does not provide mechanistic detail it is useful to generate hypotheses that can be tested experimentally.

Summary

- Up 10% of interindividual variance in cytokine responses explainable by microbiome
- parallel study found stronger influence of host genetics (av 25-50%, up to 100%!)
- Approach allows for hypothesis generation and testing
  - e.g. IFN-γ suppression by microbiota-derived tryptophol
- Criticism
  - FDR of 0.2 and no validation with another cohort means that many correlations are false positive
  - Lack of metabolic data to show that metabolite in question are actually differentially abundant (e.g. palmitoleic acid, tryptophol…)
  - the three studies are not optimally aligned, e.g. 17 different stimulations for genetics, here 5 only partially overlapping with the 17. Moreover, links between genetics, microbiome and other factors missing