The Interaction Between Gut Microbiome, Immune System and Allergy Outcomes

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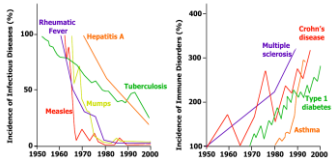
Presentation Outline

- DOHaD concept
- Establishment of the gut microbiota
- Gut microbiota and immune development
- Gut microbiota and allergic disease

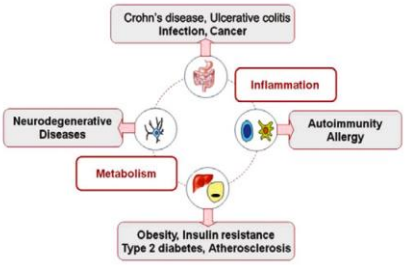
Hygiene Hypothesis: Allergic and Autoimmune Diseases



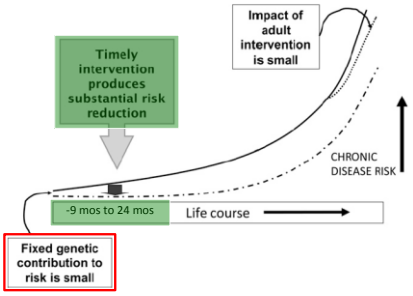
- Increased prevalence of immune mediated disorders correlated with reduced prevalence of infectious diseases
- Strachan first posed the Hygiene hypothesis in 1989
- Importance of overall microbial exposure rather than specific infections
  - Since early/mid 19th century…. Reduced exposure to microorganisms which we have lived with since the paleolithic age → Concept of evolved adaptation

Strachan DP. BMJ 1989;299:1259-60;
Bach JF. N Engl J Med 2002;347:911-20;
Rook GAW. Clin Exp Immunology; 160;70-79.

Auto-inflammatory Diseases: Common Pathways?



Early Life Programming of Disease Risk: DOHaD



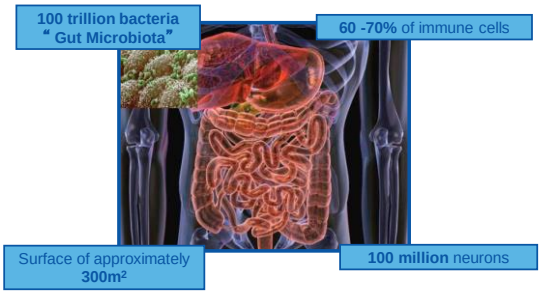
Hanson and Gluckman AJCN 2011

Environmental Risk Factors

- Microbial exposures in early life
  - Hygiene hypothesis
  - Intestinal microbiota
- Infant diet
  - Type of food first year of life
  - Timing of exposure to food allergens
- Vitamin D / UV exposure
- Immunomodulatory dietary factors
  - Omega-3 fatty acids
  - Folate?
- Pollutants

Intestinal Microbiota

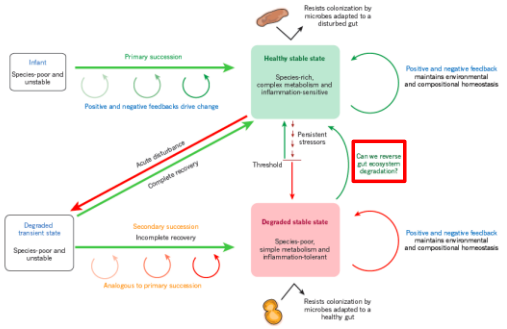
The most abundant microbial exposure during life is establishment of the gut microbiota … major impact on immune responses



Establishment of the Intestinal Microbiota

- Gut microbiota evolves rapidly from birth ➔ Relatively stable by 2 years
  - First bacterial communities (seeding bacteria) are acquired from the mother and the environment
  - Diversity increases over the first year and stablises thereafter
- Microbiota composition is influenced by early life exposures
  - Mode of delivery (cesarean vs vaginal)
  - Maternal microbiota (stress/diet during pregnancy)
  - Breast milk vs formula feeding
  - Diet
  - Sanitation and level of cleanliness
  - Antibiotic therapy
- Stable microbiota is resilient to acute environmental changes
  - Compositional homeostasis

Transitions in Gut Microbiota Composition



Lozupone et al. Diversity, Stability and Resilience of the Human Gut Microbiota Nature 2012;489:220

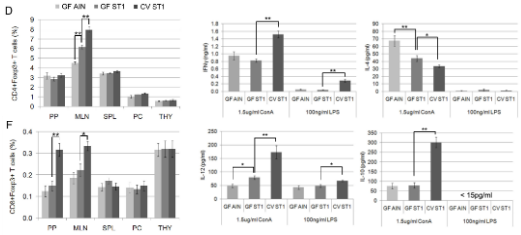
Intestinal Microbiota and Immune Development

- The intestinal microbiota plays a crucial role in development of the mucosal and systemic immune system
- Mice bred in germ free conditions have abnormal lymphoid tissues [1-4]
  - Small underdeveloped Peyer's Patches, MLNs and spleen
- Mice raised in a germ free environment fail to develop oral tolerance [5]
  - Have persistent and exaggerated Th2 dependent responses to OVA
- These abnormalities of lymphoid tissue structure and oral tolerance can be corrected by seeding the intestine with *Bacteroides fragilis* but…. *ONLY* if this occurs in the neonatal period [1,5]

1. Klaasen HL et al. Infect Immun 1993 ***61****(1): 303-6.*
2. Umesaki Y et al. Microbiol Immunol 1995 ***39****(8): 555-62.*
3. Mazmanian SK et al. Cell 2005;122:107-18.
4. Hrncir et al. BMC Immunology 2008, ***9:65***
*5. Sudo N et al. J Immunol 1997;****159****:1739-45.*

Intestinal Microbiota and Immune Regulation

- Germ free mice (that lack intestinal microbiota) [1-3]
  - Reduced numbers of FoxP3+ Treg in MLN +/- PP
  - Treg impaired suppressor function [1,2] and reduced IL10 and TGFb production[2]
  - Reduced production of IL12, IFNg, IL10; and increased production of IL4 [3]



1. Ostman et al. Eur J Immunol 2006; 2. Ishikawa et al. Clin Exp Immunol 2008; 3. Hrncir et al. BMC Immunology 2008

An altered microbiota is associated with increased risk for development of allergic disease

Intestinal Microbiota in Allergic and Non-allergic Children

- Children with eczema have altered microbiota [1-3]
  - lower counts of bifidobacteria and lactobacilli
  - higher counts of *S aureus, C difficile* and *E coli*
- These differences *precede* the onset of allergic disease [4-6]
  - lower counts bifidobacteria and enterococci at 1 mos
  - lower counts of bifidobacteria and bacteroides at 12 mos
  - higher counts of *C difficile* and *E Coli* at 3 weeks and 3 mos
  - more often colonised with *S aureus* at 6 mos

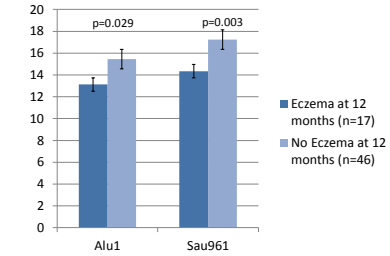
1. *Bjorksten B et al. Clin Exp Allergy 1999;29:342-6.*
2. *Kalliomaki M et al. J Allergy Clin Immunol 2001;107:129-34.*
3. *Sepp E et al. Clin Exp Allergy 2005;35:1141-6*
4. *Kalliomaki M et al. J Allergy Clin Immunol 2001;107:129-34*
5. *Bjorksten B et al. J Allergy Clin Immunol 2001;108:516-20.*
6. *Penders J et al. Gut 2007;56:661-7*

Intestinal Microbiota in Allergic and Non-allergic Children

- The composition of bifidobacterium flora is also different in children with allergic disease
  - Specific strain differences *vary in different locations*
- Scandinavia
  - allergic subjects have predominance of *B adolescentis (adult-type)* [1]
  - healthy infants have predominance of *B bifidum and B catenulatum / pseudocatenulatum* [1,2]
  - reduced adhesion to human intestinal mucus [3]
  - induce less IL10 production in vitro [4]
- *Japan* [5,6] *and New Zealand* [7]
  - Allergic subjects higher levels of *B bifidum* (Japan) and *B catenulatum (Japan, NZ)*

[1] Ouwehand AC et al. J Allergy Clin Immunol 2001;108:144-5; [2] Stsepetova J et al. FEMS Immunol Med Microbiol 2007;51:260-9; [3] He F, Isolauri E, Salminen S et al. FEMS Immunol Med Microbiol 2001;30:43-7; [4] He F, Morita H, Hashimoto H et al. J Allergy Clin Immunol 2002;109:1035-6; [5] Songjinda P et al. Biosci Biotechnol Biochem 2007;71:2338-42; [6] Suzuki S et al. Clin Exp Allergy 2007;37:506-11; [7] Gore C et al. J Allergy Clin Immunol 2008;121:135-40

PEPS cohort: Reduced Microbial Diversity at Day 7 in Infants with Eczema Ever at 12 months



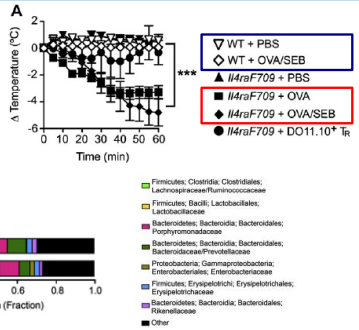
Ismail et al. Pediatr Allergy Immunol 2012;23:674-81

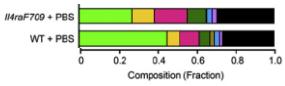
Abrahamsson et al. J Allergy Clin Immunology 2012;129:434
Wang M et al. J Allergy Clin Immunol 2008;121:129-34

Altered microbiota in mice susceptible to food allergy

Il4raF709 mice

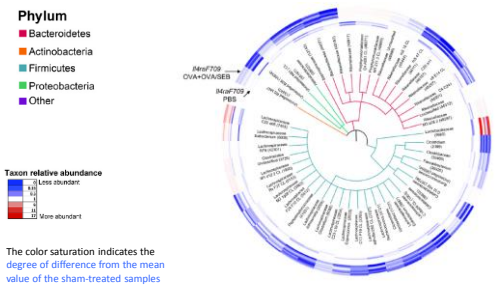
- Carry a gain of function mutation in IL4R a chain
- Susceptibility to experimentally induced food allergy





Noval Rivas M et al. JACI 2013;131:201-12

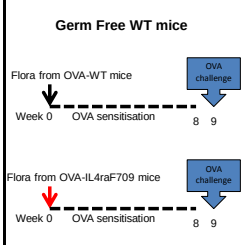
Sensitisation to OVA in IL4raF709 mice induces a specific microbial signature

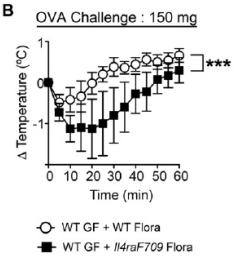


The color saturation indicates the degree of difference from the mean value of the sham-treated samples

Noval Rivas M et al. JACI 2013;131:201-12

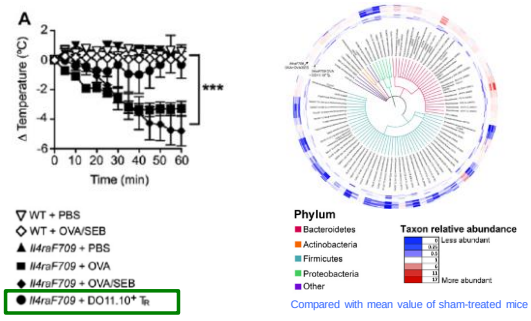
Intestinal microbiota from sensitised Il4raF709 mice transmits susceptibility to experimentally induced food allergy





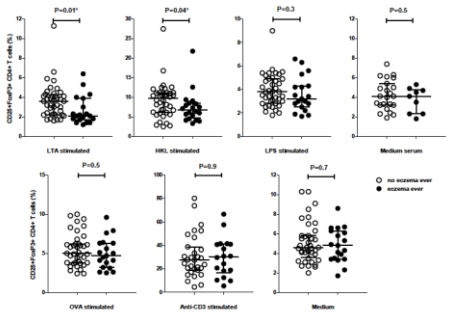
Noval Rivas M et al. JACI 2013;131:201-12

Transfer of Treg cells can prevent food allergy and induces a tolerogenic microbial signature



Noval Rivas M et al. JACI 2013;131:201-12

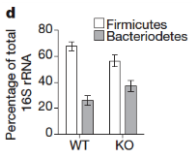
Infants with eczema have reduced Treg capacity in response to TLR stimulation at birth



Ismail et al. Pediatr Allergy Immunol (In press)

iTreg can Influence Microbiota

- iTreg are important for control of unwanted allergic inflammatory responses at mucosal sites
  - Absence of iTreg in CNS1- mice was associated with intestinal and lung Th2 inflammation
- iTreg help maintain a 'normal' microbial community in the gut
  - Absence of iTreg in CNS1- mice resulted in altered gut microbial communities
  - enrichment of phylum TM7, genus Bacteroidetes Alistipes
  - overall decrease in the ratio of Firmicutes to Bacteroidetes



Percentage of total 16S rRNA gene sequences of the Firmicutes and Bacteroidetes phyla in stool from individually housed CNS1- (n=9) and WT (n=6) littermate mice.

Josefowicz et al. Nature 2012

Summary

- The rapid rise in non-communicable diseases has occurred as a result of environmental changes associated with the modern lifestyle; in particular, reduced microbial exposures have led to altered intestinal microbial signatures that are associated with allergic disease risk
- The intestinal microbiota plays a critical role in immune development and early life immune programming
- Alterations in the intestinal microbiota in the first weeks of life are associated with development of allergic diseases in later life
- In mouse models, disease risk can be conferred by transfer of disease associated microbial signatures; and conversely, protection against disease can be conferred by favourable microbial signatures
- Infants who develop eczema by 1yr have reduced Treg response to TLR stimulation from the time of birth
- Modulation of the intestinal microbiota in early life may offer a novel approach to prevention or treatment of allergic disease; and may be most beneficial in infants at increased risk of allergic disease