

Allergy development – intrauterine and onwards

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IgE 50 years, 6th October 2017

Presentation layout

IgE symposium
Immunology section
Intrauterine environment & Allergy



IgE in the intrauterine environment



Intrauterine/neonatal microbial
environment –
Immune profile in the offspring?
Relevance to allergy?

IgE in the intrauterine environment

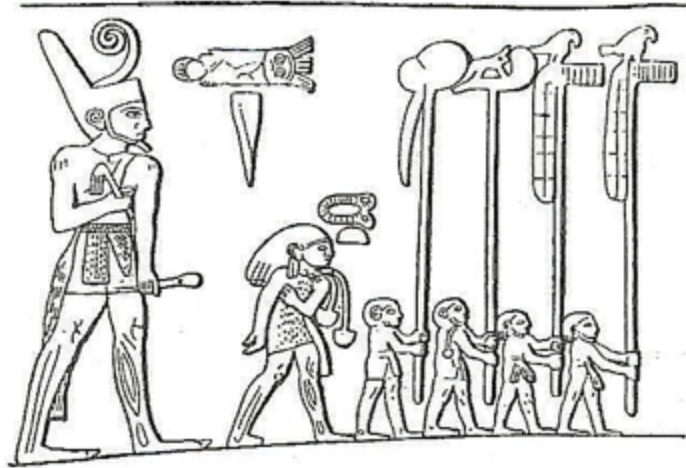


Figure 1. The Pharaoh in a procession as depicted on an Egyptian ceremonial slate of 3400 B.C. The fourth of the standards represents the royal placenta with the umbilical cord.

IgE in the intrauterine environment – what was known?



- Allergic diseases often present in early years
- Maternal allergy is considered to be a stronger risk factor than paternal allergy
- IgE present in cord blood
 - Origin?
 - Predictor for allergy?
- -> **Suggested a role of the intrauterine environment**

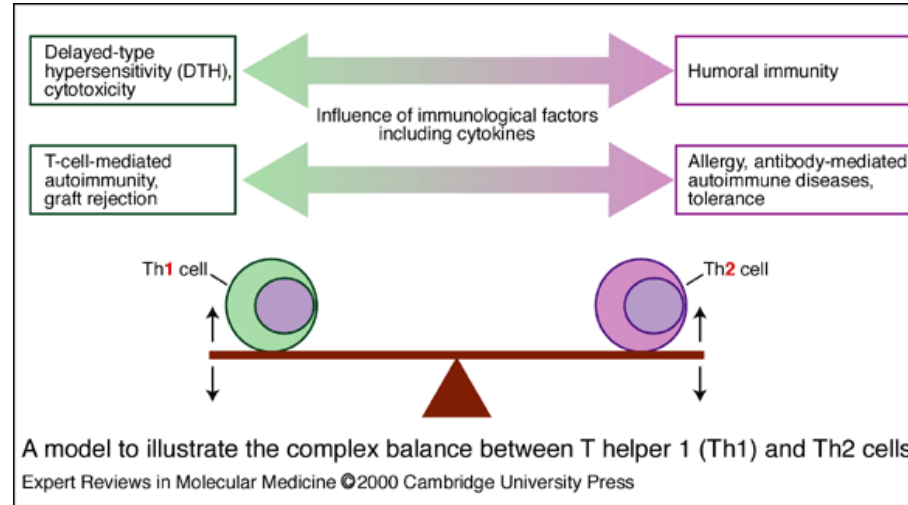
IgE in the intrauterine environment – what was known?



- *Cederqvist et al Am J Obstet Gynecol 1976:*
 - IgE in the amniotic fluid
- *Jones et al Lancet 1998:*
 - Exposure to IgE in the intrauterine environment
 - Correlation between maternal plasma- and amniotic fluid levels of total IgE
 - -> Postulated fetal swallowing of IgE

When life was easy: Th1 vs Th2

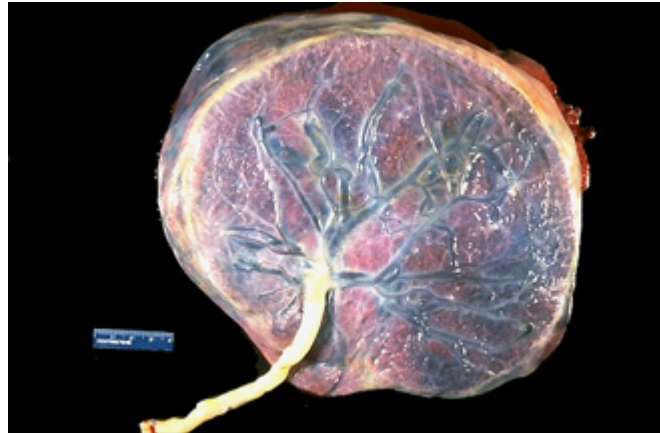
"A Th2 environment promotes allergy"



- *Umetsu et al J Immunol 1988*: Functional heterogeneity among **human** inducer T cell clones
- *Maggi et al Eur J Immunol 1988*: Profiles of lymphokine activities and helper function for IgE in **human** T cell clones
- *Herz et al Eur J Immunol 2000*: Maternal allergy promotes neonatal Th2 immunity (murine model)

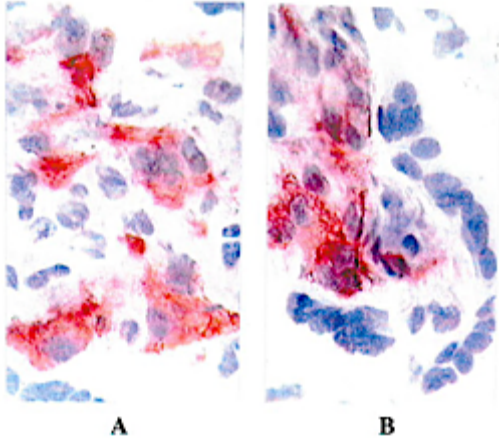
IgE in the intrauterine environment

- Does the local environment in the placenta contain IgE? On which cells? Does this differ between allergic and non-allergic mothers?

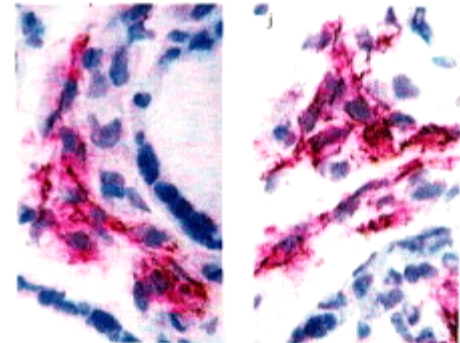
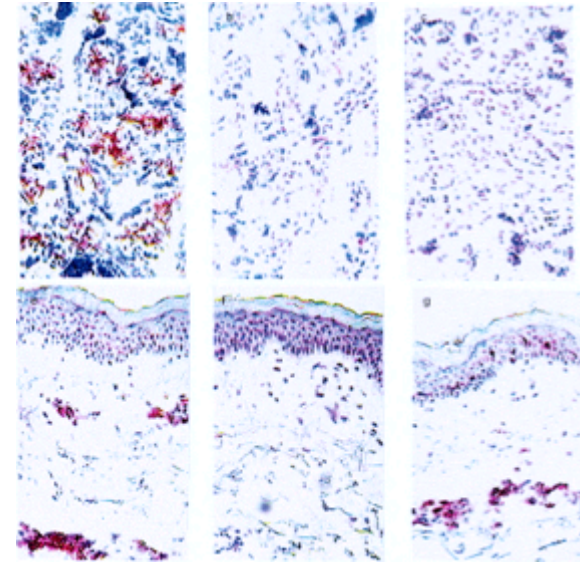
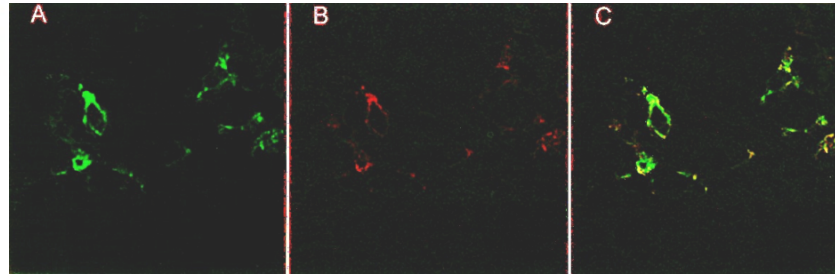


IgE in the human placenta

Term placentas (n=86) from a prospective allergy cohort
Immunohistochemical stainings for IgE & receptors

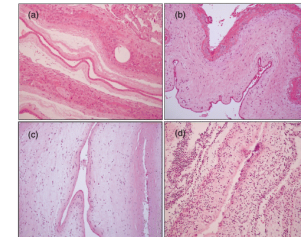


No evidence of local
placental IgE production

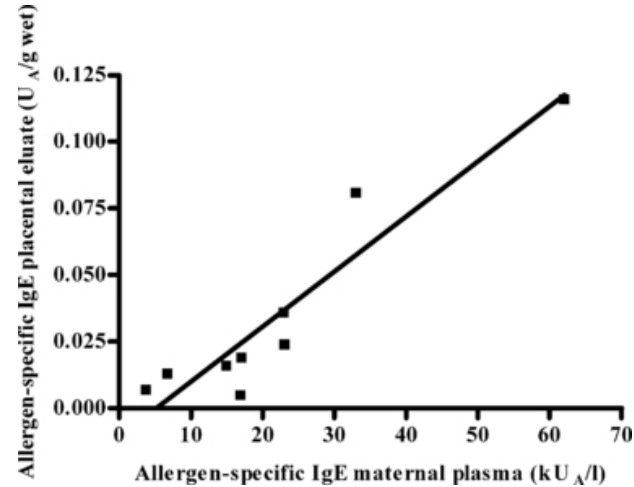
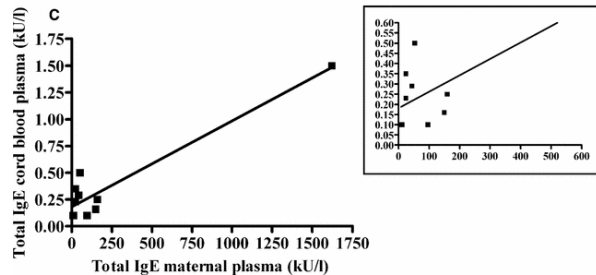
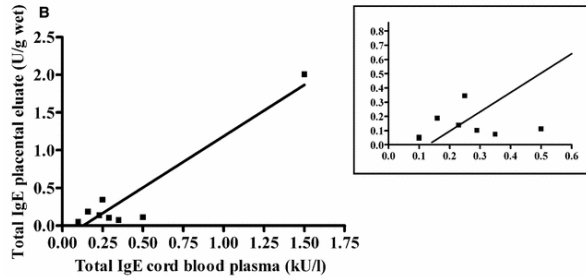
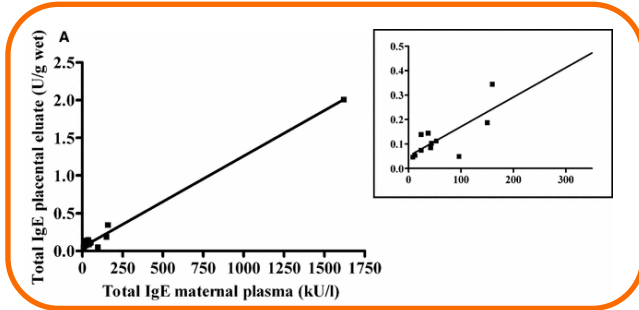


Will allergy or infection influence placental IgE?

- Placental IgE is **independent** of:
 - Maternal allergy
 - Sverremark-Ekström et al *Clin Exp Immunol* 2002
 - Malaria infection
 - Rindsjö et al *Clin Exp Immunol* 2006
 - Chorioamnionitis
 - Rindsjö et al *Clin Exp Immunol* 2006

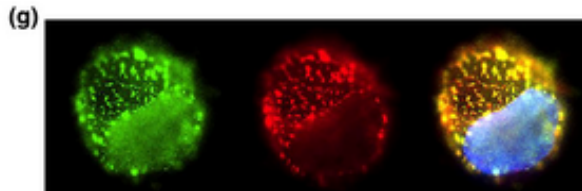
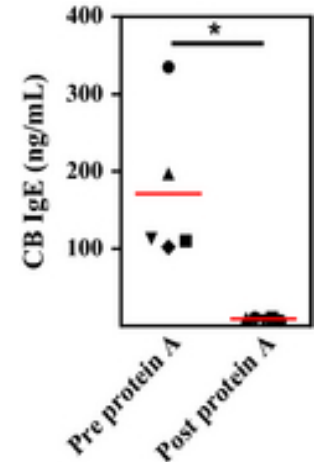
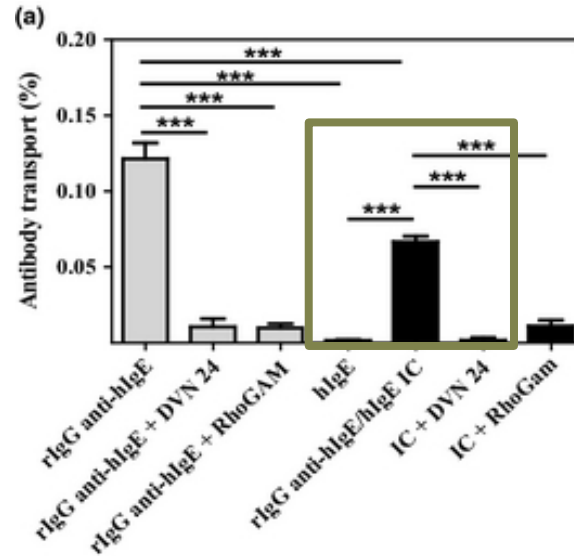
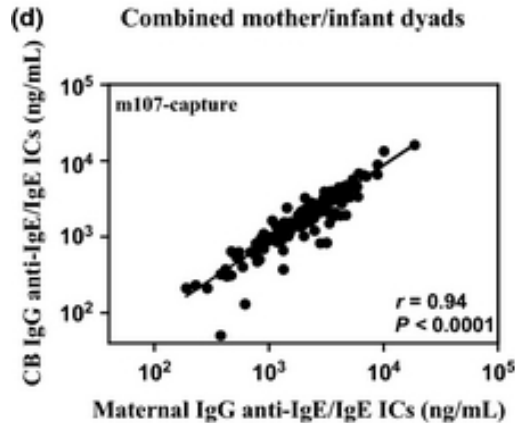


IgE in the human placenta: maternal or fetal?



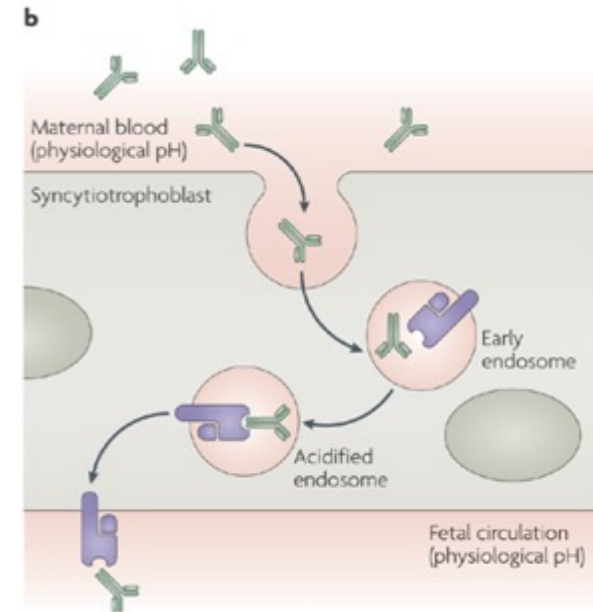
Joerink et al Allergy 2009

Transplacental passage of maternal IgE via cRn in the form of IgG-IgE immune complexes



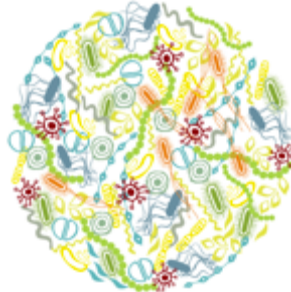
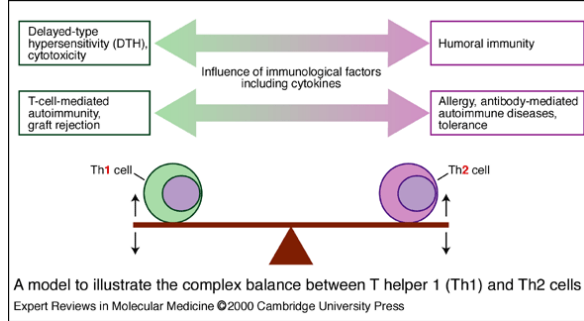
IgE in utero– beneficial, harmful, or?

- “Mucosal antibody”?
- Protecting the fetus against harmful substances?
- “In symbiosis” with the Hofbauer cells, promoting their survival?
- Maternal origin (?), Promoting allergy?

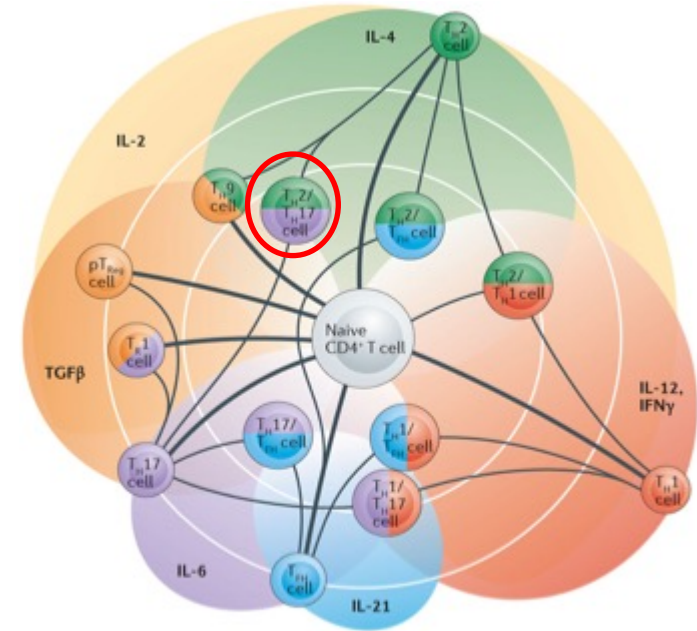
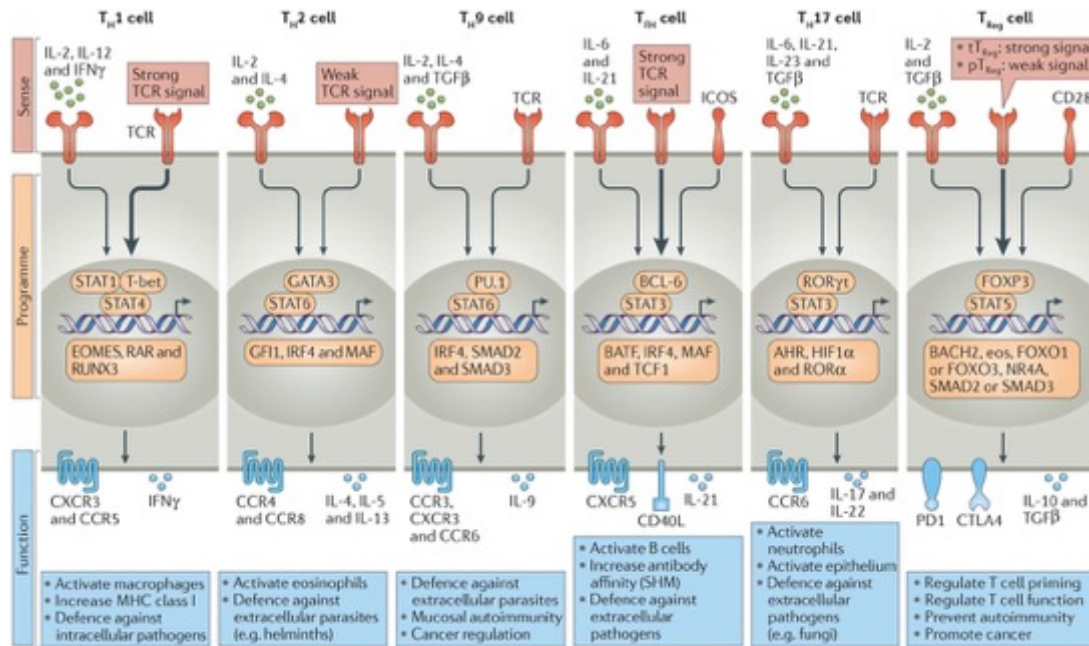


Nature Reviews | Immunology

Intrauterine/neonatal microbial environment – Immune profile in the offspring? Relevance to allergy?



T cell subsets today – from Th1/Th2 to Th“X” and a great plasticity

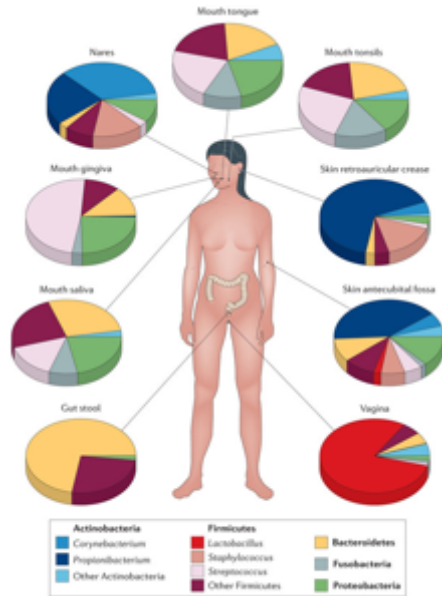


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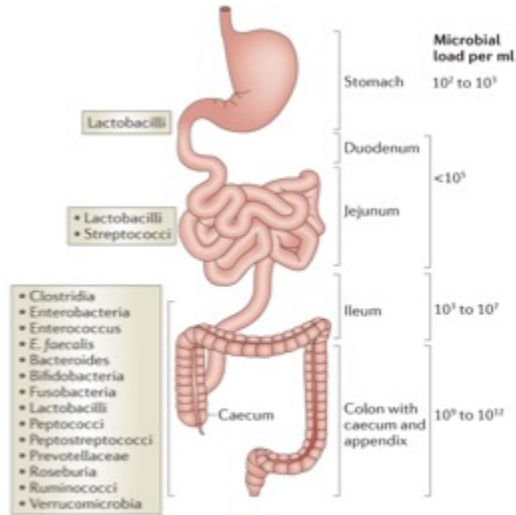
DuPage & Bluestone Nature Rev Immunol 2016



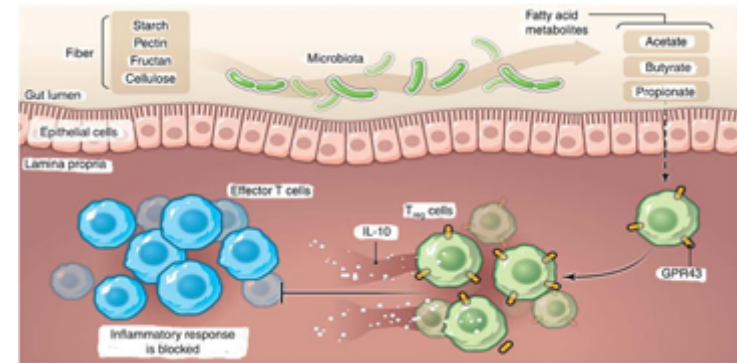
Microbiota & immune balance – the intestine in focus



Nature Reviews | Genetics

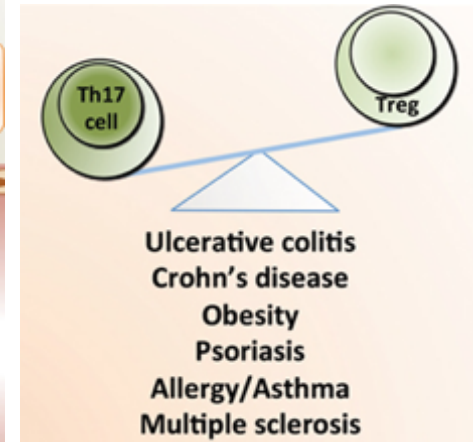
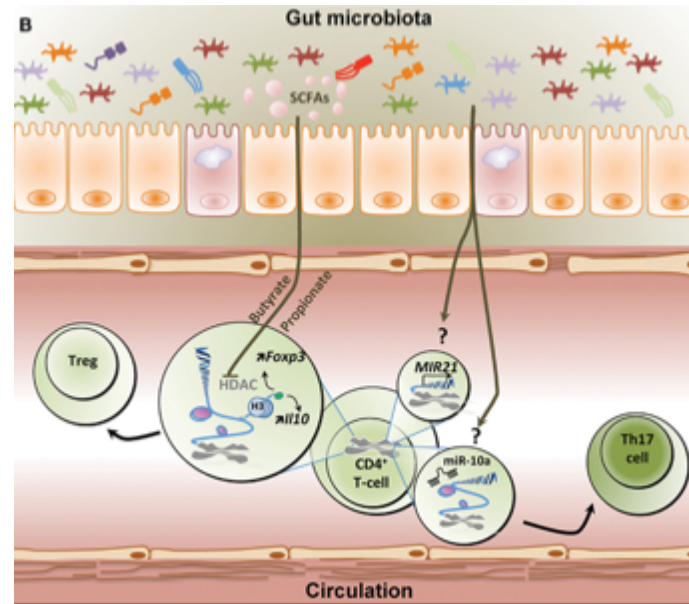
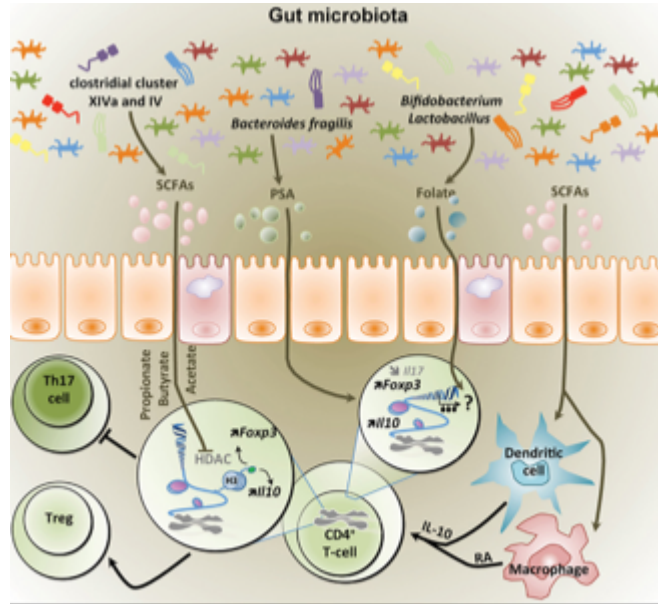


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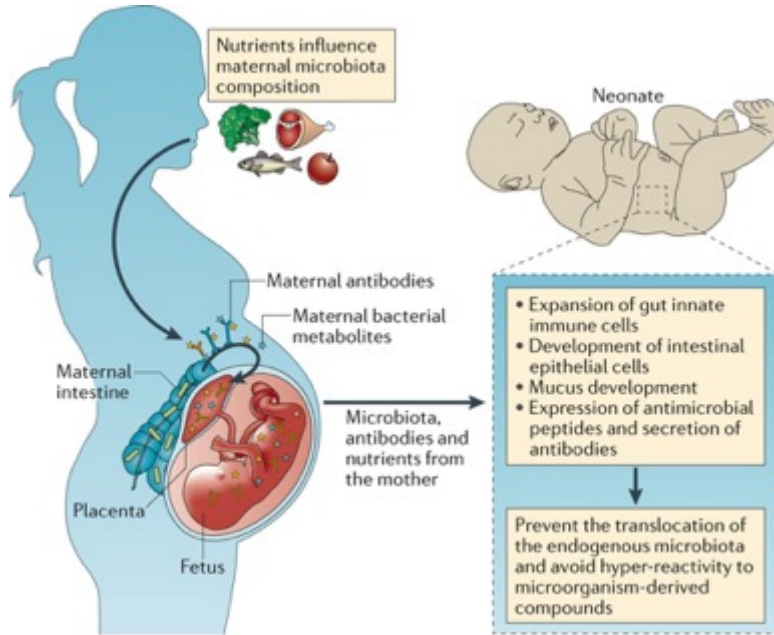
Lasken & McLean Nat Rev Genetics 2014
 Mowat & Agace, Nat Rev Immunol 2014
 Walker Pediatr Res 2017

Bacterial metabolites influence the epigenome of T-cells

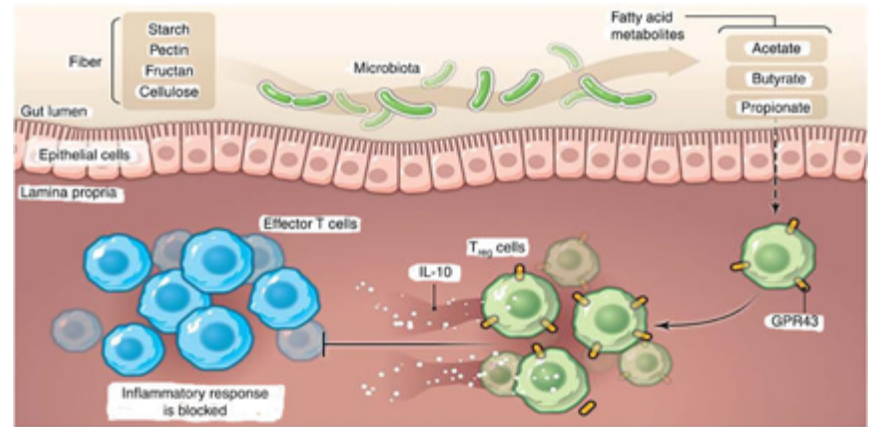


Luo et al Front Immunol 2017

Microbiota, intrauterine environment and immune development



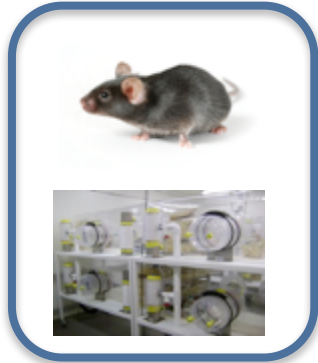
Nature Reviews | Immunology



Gomez de Agüero et al Science 2016
Macpherson et al Nature Rev Immunol 2017

Geuking et al Immunity 2011
Walker Pediatr Res 2017

Microbiota-mediated immune regulation *in vivo*



NH_L

No allergic heredity

Lactobacilli⁺ microbiota

Low risk of sensitization and allergy at 5 years

AH_L

Allergic heredity

Lactobacilli⁺ microbiota

Low risk of sensitization and allergy at 5 years

AH

Allergic heredity

Lactobacilli⁻ microbiota

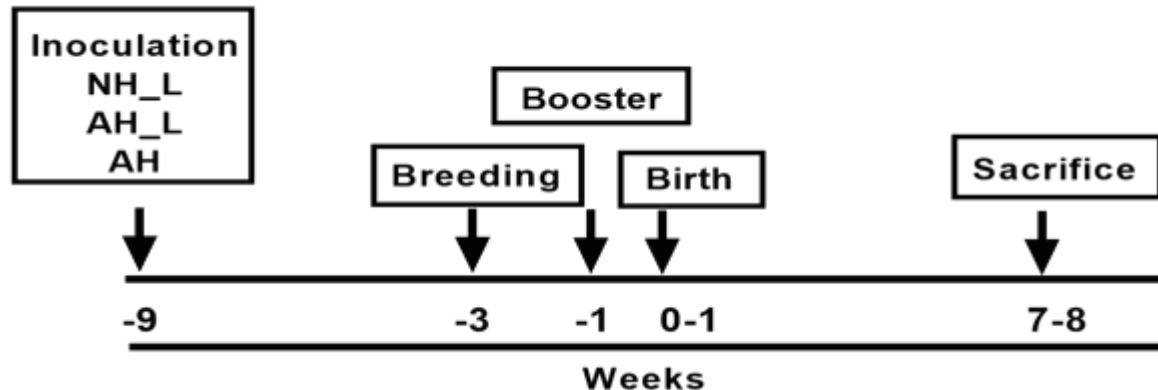
Allergic at 5 years

Sjögren et al Clin Exp Allergy 2009

Johansson et al PLoS one 2011

Björkander et al JACI 2016

Björkander et al manuscript 2017



Petursdottir, Nordlander et al submitted 2017

A gut microbiota connected to a high allergy risk in children, promotes a strong Th17 immunity

Petursdottir, Nordlander et al 2017

The mice “tolerate” the human microbiota well – no signs of intestinal inflammation

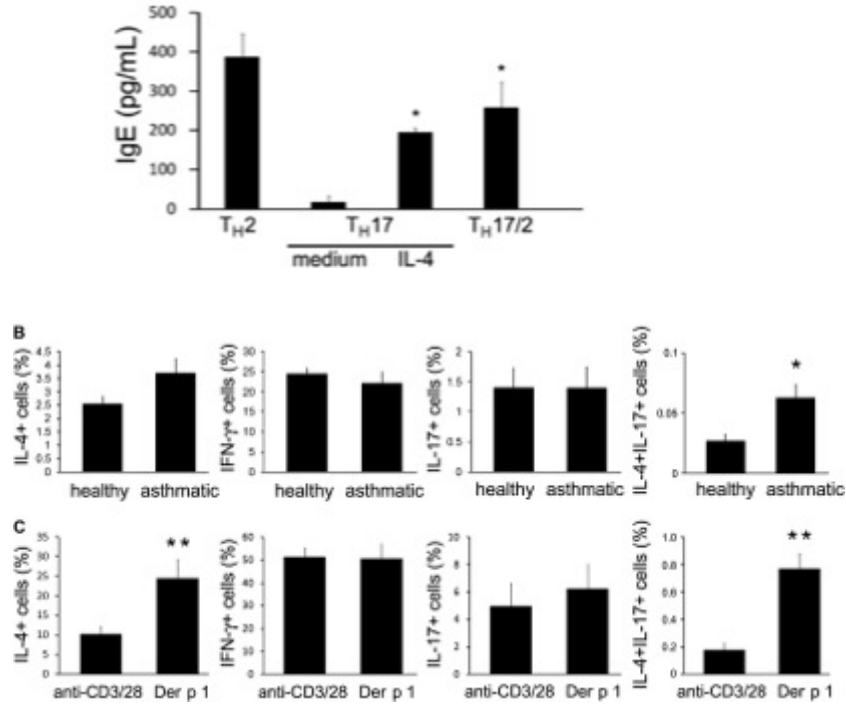
Petursdottir, Nordlander et al 2017

**Significant differences in “allergy-protective” and “allergy-risk/Th17-promoting” floras
but it is not a matter of diversity.....**

Petursdottir, Nordlander et al 2017

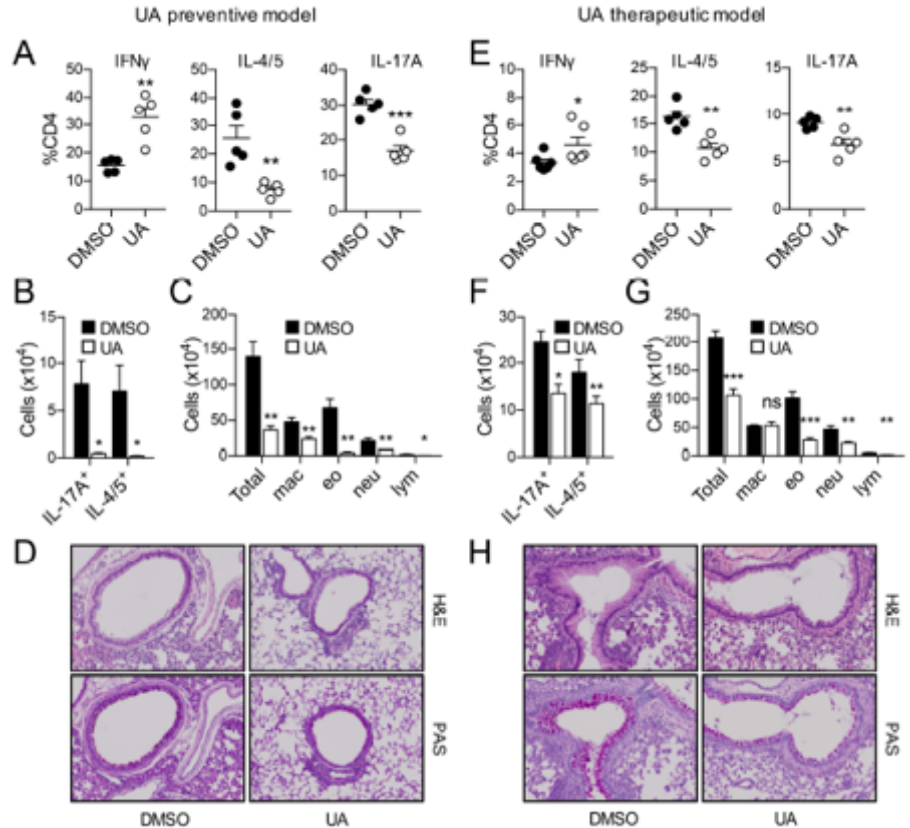
Th17/2 cells contribute to allergic responses

Suppressed by targeting ROR γ t

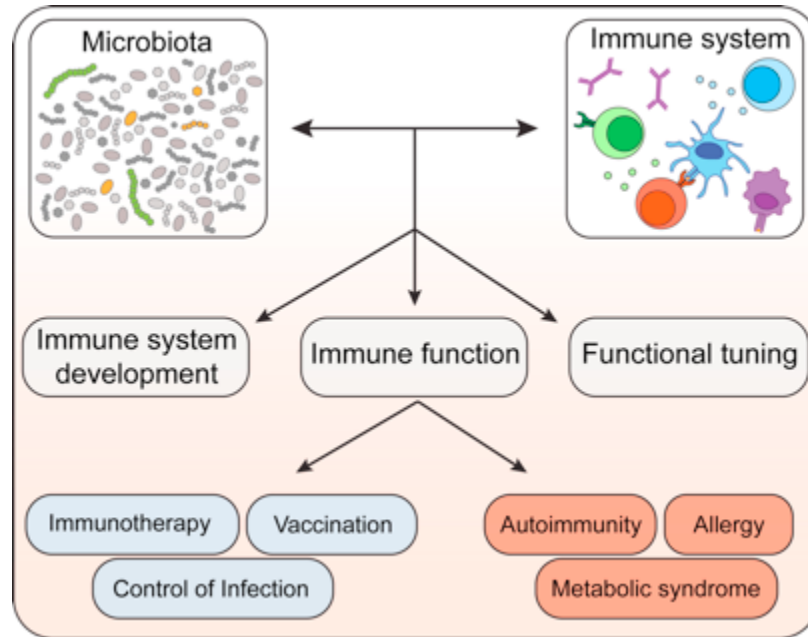


Cosmi et al JACI 2010

Na et al JACI 2017



Microbiota and the immune system



Belkaid & Harrison Immunity 2017

Acknowledgements

Gut microbiota & immune maturation:

Sophia Björkander
Sofia Nordlander
Dagbjört Petursdottir
Khaleda Rahman Qazi
Yeneneh Haileselassie
Claudia Carvalho-Queiroz

Velmurugesan Arulampalam – Karolinska Institutet
Stefan Roos - Biogaia
Caroline Nilsson – Sachs Children's Hospital
Jan-Olof Persson & Klas Udekwu– Stockholm University
Diarmaid Hughes- Uppsala University

IgE in placenta:

Ulrika Holmlund
Ingeborg van der Ploeg
Bengt Sandstedt
Caroline Nilsson
Gunnar Lilja
Annika Scheynius

Vetenskapsrådet
Ragnar & Torsten Söderbergs Stiftelser
Engkviststiftelsen
Hjärt-Lungfonden
Cancer och allergifonden
Stockholms Universitet

