Nutrition and early immune development

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The immune system ....
... is a cell and tissue system that protects the individual from invading pathogens.
A well functioning immune system is key to providing robust defence against pathogenic organisms.
It .....  

... distinguishes “self” from “non-self”
Every day we eat animal and plant materials -> continuous chronic exposure to “non-self”

Our gi tract, other mucosal surfaces and skin are covered in billions of micro and macro organisms -> continuous chronic exposure to “non-self”
A well functioning immune system is key to providing robust defence against pathogenic organisms and to providing tolerance to non-threatening organisms, to food components and to self.
Host defence against threatening (micro)organisms

Tolerance of self, food & non-threatening (micro)organisms
The immune response ....

- The individual’s response to infection by bacteria, viruses, fungi, and parasites
- Involved in protection against growth of cancer cells
- Distinguishes “self” from “non-self” => Tolerance
- Typified by cellular interactions and movement of cells to sites of infection
- Normally it is protective (and so beneficial)
- It includes both non-specific, innate (natural) responses and specific, acquired responses
- Includes a component of memory
- Involves various cell types including antigen presenting cells (especially dendritic cells), macrophages and T and B lymphocytes
The four general functional features of the immune system

• Exclusion barrier
• Identification of “non-self”/Tolerance of “self”
• Elimination
• Memory
Interaction amongst immune cells

B cells

Th cells

NK cells

Tc cells

Antibodies

Bacteria

Phagocyte

Virus infected cell

Activate

Activate

Activate

Activate

Antigen presentation

Antigen presentation

Lysis
It is clear that having an immune system that works well is the key to:
- preventing infections
- controlling the effects of being infected
- dealing with both harmful and harmless environmental constituents
Host defence against threatening (micro)organisms

Tolerance of self, food & non-threatening (micro)organisms

Susceptibility to infection

Imbalance

Immune-mediated disease
The concept of immune fitness

• a resilient immune system ......
• with an inbuilt capacity to adapt to challenges by ..... 
• establishing, maintaining and regulating ..... 
• an appropriate immune response
The immune system over the lifecourse

• Babies are born with an immature immune system -> this will develop over time with exposure to maturation factors (e.g. in breast milk) and with increasing exposure to new antigens (i.e. to new foods and to new pathogens)

• The function of the immune system declines with old age – called immunosenescence (depletion of naïve cells due to cumulative lifetime antigen exposure?)
Immune competence changes with age

Threshold for increased risk of infections and poor response to vaccination
Immune development begins early (in utero)

- T cells are present in developing thymus by about 12 weeks of gestation
- Lymphocytes with surface Ig are present in 2nd trimester
- An adaptive immune capability is present at birth but it is not fully or properly functional
Innate immune cells reach adult levels by 12 months

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<th>Birth</th>
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Factors influencing immune development after birth

- Environmental microbes and their products
  - Hygiene hypothesis
- The (endogenous/acquired) microbiome: gut, skin, respiratory
- Diet: many nutrients (vitamins, minerals, essential amino acids, PUFAs) and non-nutrients (e.g. nucleotides, oligosaccharides, gangliosides, ……)

NOTE: In early life, diet = breast milk
### Relevant components in human milk

#### Protective Factors
- Secretory IgA, IgM, IgG
- Lactoferrin
- Lysozyme
- Complement C3
- Leukocytes
- Antiviral mucins, GAG
- Nucleotides
- Oligosaccharides

#### Cytokines and Anti-Inflammatory Factors
- Tumor necrosis factor
- Interleukins
- Interferon
- Prostaglandins
- α-anti-chymotrypsin
- α -anti-trypsin
- Platelet-activating factor: acetyl hydrolase

#### Growth Factors
- Epidermal (EGF)
- Nerve (NGF)
- Insulin-like (IGF)
- Transforming (TGF)
- Polyamines

#### Hormones
- Feedback inhibitor of lactation (FIL)
- Insulin
- Prolactin
- Thyroid hormones
- Corticosteroids ACTH
- Oxytocin
- Calcitonin
- Parathyroid hormone
- Erythropoietin

#### Digestive Enzymes
- Amylase
- Bile acid-stimulating esterase
- Bile-stimulating lipases
- Lipoprotein lipase
- Ribonuclease

#### Transporters
- Lactoferrin (Fe)
- Folate binder
- Cobalamin binder
- IgF binder
- Thyroxine binder
- Corticosteroid binder

#### Others
- Casomorphins
- δ-sleep peptides
- Leukocytes
How does breast milk help baby’s immunity?

Protective Factors
- Secretory IgA, IgM, IgG
- Lactoferrin
- Lysozyme
- Complement C3
- Leukocytes
- Cytokines & growth factors
- Antiviral mucins
- Gangliosides
- Oligosaccharides
- Nucleotides

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Host defence against threatening (micro)organisms

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Susceptibility to infection

Imbalance

Immune-mediated disease
- Immature APCs/DCs
- Sterile/germ free
- No memory
- No induced Th cell bias
- Innate responses

- Trained mature APCs/DCs
- Endogenous microbiota
- T and B cell memory
- Th1/Th2 /Treg responses
- Adaptive responses
34% of under-five deaths are from diarrhoeal disease and acute respiratory infections.

Sources:
Infection impairs infant growth
Susceptible to infections

- Immature APCs/DCs
- Sterile/germ free
- No memory
- No induced Th cell bias
- Innate responses

Healthy response

- Trained mature APCs/DCs
- Endogenous microbiota
- T and B cell memory
- Th1/Th2 /Treg responses
- Adaptive responses

Susceptible to allergies
Infant benefits of breastfeeding:
- reduces risk of neonatal infections
- promotes development of the immature immune system and gut
- reduces risk of infant allergy
Host defence against threatening (micro)organisms

Susceptibility to infection

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Immunologically mediated diseases
The Atopic March - Prevalence of Allergic Manifestations By Age

- Asthma
- Atopic dermatitis
- Allergic rhinitis
- Gastro-intestinal allergies
- Food allergens
- Aeroallergens

Age (yrs): 0.5, 1, 3, 7, 15
Immunity & Allergy: Tolerance versus inflammation

Healthy Infant

Antigen or Allergen

Immune System

Immunity or Allergy

Recognized as “harmless”

Oral tolerance

Non-responsiveness

Recognized as “harmful”

Inflammation

Hyper-responsiveness

Break of tolerance

Acquisition of tolerance
Risk factors for the development of allergies

Hereditary Factors

- Family History of allergy & early sign of eczema
- Risk to develop allergy: 15%-70%

Gut microbiota challenge

- C-Section
- Global Prevalence:
  - EU: 15%-35%
  - Asia Urban: >50%

Antibiotic Use

- Use in infancy & childhood:
  - Up to 10 - 20 courses

Environmental challenge

- Pollution
- Increased risk of allergy:
  - Up to 20%
Intestinal Immune System

The human gastrointestinal tract contains 10 times more bacterial cells than there are human cells in the body -> you are 90% bacteria!
Bifidobacteria are early colonizers of the human gut.
Microbial colonisation plays a role in gut and immune maturation
Diversity is mainly influenced by:
- maternal microbiota
- mode of delivery
- feeding type

With the introduction of other foods, a diverse microbial population develops.

Arrieta et al. (2014) Front. Immunol. 5, 427
Filthy

(Just building my immune system, Mum)

Is too little dirt causing the allergy epidemic?
A prebiotic is a selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health.
Prebiotics and bifidogenic gut colonization


Term infants after 28 days formula feeding

log 10 of CFU/g wet faeces (median, IQR)

Bifidobacteria

Lactobacilli

Breast-fed infants

eHF Whey

& GOS /FOS

eHF Whey

& GOS /FOS

Prebiotics and prevention of infections

Arslanoglu et al. (2007) J. Nutr. 37, 2420-2424
Prebiotics and prevention of allergy

Cumulative incidence of atopic dermatitis

After 6 months

- scGOS/lcFOS (n=102) 9.8%
- Control (n=104) 23.1%

P=0.014

After 2 years

- scGOS/lcFOS (n=66) 13.6%
- Control (n=68) 27.9%

P<0.05

After 5 years

- scGOS/lcFOS (n=40) 10%
- Control (n=49) 26.5%

P<0.05

Presence of any allergy-related symptom

How do prebiotics act?

1. Competition Exclusion
2. Stimulation of mucous production
3. Promotion of sIgA production
4. Tissue repair
5. Promotion of Treg cells and tolerance
6. Epithelial integrity
7. Inhibition of inflammation and NF-κb

Infant formula with prebiotics promotes a metabolic profile closer to that of breast fed infants

Reduce fecal pH  
Fecal short chain fatty acids

Infant formula with prebiotics increases fecal sIgA level during the first 6 months of life

The WAO guideline panel suggests using prebiotic supplementation in not-exclusively breastfed infants and not using prebiotic supplementation in exclusively breastfed infants.

12 out of 19 publications included for the systematic review were studies with the prebiotic mixture scGOS/lcFOS.
How does breast milk help baby’s immunity?

**Protective Factors**
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**Others**
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- δ-sleep peptides
An effective immune system is key to defense against pathogenic organisms.

The immune system also determines tolerance.

Babies are born with an immature immune system that requires “education” soon after birth.

Allergy represents an inappropriate education of the immune system.

Breast milk provides many nutrients and other factors that promote immune education and acquisition of a protective gut microbiota.
Non breast fed infants are likely to not receive sufficient “immune educating” factors and to have gut dysbiosis -> increased risk of infections and allergies

Prebiotics promote colonization of protective bacteria -> SCFA -> immune education

But prebiotics are a concept not a unique agent and not all prebiotics are the same: some prebiotics added into infant formula have been shown to result in fewer infections and allergies and a normalized immune response

Prebiotics are just one example of how nutritional approaches can be use to assure immune fitness early in life