Prenatal events in the development of Food Allergy

PROF SUSAN PRESCOTT
Changing allergy patterns in developed regions

Food allergy: a new wave in the allergy epidemic

RESPIRATORY ALLERGY EPIDEMIC 20+ year lag FOOD ALLERGY EPIDEMIC

Inhaled allergy test + (and hay fever)

Asthma

Prevalence (%)

Food allergy test + Eczema Food allergy


YEAR

Prevalence (%)

0 10 20 30 40

e.g Australia, Singapore, New Zealand, Hong Kong
Dramatic increase in food allergy and eczema in the last 10 years

Mullins, MJA 2007; 186: 618-621 (Australian data)
Dramatic increase in severe reactions (anaphylaxis)

5-fold rise in preschoolers over 10 yrs

Mullins, MJA 2007; 186: 618-621 (Australian data)
Food sensitisation: a very early event

• RCT: start egg/placebo at 4-6 months
• 22% reaction rate at randomization (prior to the intervention)
• 1.2% anaphylaxis Rx adrenaline
• On first known oral exposure to egg
• ‘Early feeding’ already too late in these children

Implies much earlier allergen exposure: pregnancy, lactation, transcutaneous
Neonatal differences in immune function point to the importance of in utero events

Presymptomatic differences at birth in allergic individuals:

- **Increased inflammatory responses**
  - Prescott JACI 2008;122:391

- **Immature Th1 function**

- **Immature T reg function (?)**
  - Smith/Prescott 2008;121:1460
  - Schaub 2008;121:1491

Gene-environmental interactions in utero. Epigenetic influences?
Fetus: highly developed regulatory responses

- Not an ‘immature’ version of adults \(^1\)\(^-\)^\(^2\)
- Highly responsive to antigens
- Strong bias to Treg differentiation (tolerogenic milieu: TGFβ, TSLP)
- Higher % circulating Treg than adults\(^3\)

→ Wave of promiscuously responsive cells
→ Gives rise to a broad repertoire of Treg (self antigens)

Does tolerance to exogenous antigens (allergens) begin during this period?

- Allergens cross the placenta
  → detected in cord blood, placenta and amniotic fluid

- Fetus can generate long-lived CD4+CD25+FoxP3+ Tregs
  → to exogenous antigens (alloantigens, microbial Ag)\(^1,2\)
  → can modulate postnatal responses

- Fetal allergen-specific responses
  → generate Treg in vitro\(^3\)

The role of the thymus?

- **Autoreactive clones**
  - Deleted (high affinity)
  - Converted to Treg (medium affinity)
    → periphery (tolerance)

- **Surprising new studies:**
  - T cells/DC re-enter thymus (physiological)
    → deliver Ag from periphery \(^1\)
  - DC can carry allergen (OVA) from tissues
    → to the thymus (experimental) \(^2\)
    → regulatory response

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Challenges notion of unidirectional role of thymus: New perspectives for tolerance to exogenous Ag?
New evidence of differences in thymic development in allergy

- Th2 milieu in neonatal thymus
- Capacity for Treg: $\propto$ TSLP level

- **Atopic children**
  - Reduced Treg (% and function)
  - Reduced TSLP
  - Evident in neonatal period
    - reflects in utero environment

- **Postnatal period**
  - Breast milk IL-7 crosses intestine
  - Influences thymic size / T cell function


**Environmental effects on thymic milieu may alter T reg development**
Common risk factors
For many modern diseases

Δ microbial balance
Δ dietary profile
  ↧ ↑ Saturated fat
  ↧ ↓ Dietary fibre
  ↧ ↓ n3/n-6 PUFA
  ↧ ↓ Fresh foods
Δ Sunlight (vitamin D)
Δ Exercise patterns
Δ Pollutants
  – Smoking
  – Toxins & POPs
  – EM radiation?

Inflammation

= Common interventions for prevention

Allergy
Autoimmunity
Obesity
Metabolic disease
Diabetes
Cardiovascular Disease
Neurodegenerative Disease
Inflammatory Bowel Disease
Cancer
Central role of the gut and nutrition
In maintenance of immune and metabolic homeostasis
(adverse exposures lead to inflammation and metabolic dysregulation)
Exposures in very early development can increase risk of future diseases

Early environment
(diet, microbes, toxins, stress)

Risk of later disease
(heart disease, obesity, dementia, diabetes, allergy, asthma)
How is this happening?

Early exposures
(diet, microbes, toxins, stress)

Changes in gene expression

The environment can change the ‘epigenetic code’ which determines patterns of gene expression in each cell.

Risk of later disease
(heart disease, obesity, dementia, diabetes, allergy, asthma)
Good news: ‘plasticity’ means opportunity for change

Opportunities may be greater during early development

Changing pattern of gene expression

Changing disease predisposition

Opportunities for change! (Prevention and re-programming)
Logical preventive approaches
Restoring environment balance

↑ Pollutants ↓ Reduce avoidable exposure (individual and societal)
↑ Pharmaceutics ↓ Reduce unnecessary use (individual and HCP)
↓ Microbial exposure ↑ Strategies to restore balance probiotics, prebiotics, other?
↓ Traditional diets ↑ Anti-inflammatory nutrients n-3 PUFA, fibre, antioxidants,
↑ Sedentary lifestyles ↑ Behavioural strategies exercise, ‘de-stress’, sun in moderation, vitamin D?
Smoking and Pollutants

Cigarette Smoking:
- MANY adverse effects on the fetus
- effects on placental function
- abnormal lung development / asthma risk

Diesel exhaust particles:
- immune effects and increased asthma risk

Organic pollutants (pesticides / industrial chemicals):
- persistent and lipid soluble
- detected in cord blood, placenta and breast milk
- suspected role in immune disease

All have epigenetic effects
Avoidance strongly recommended
Other adverse modern exposures

The public has many candidates:
- Chemicals and food additives
- Cleaning products
- Electromagnetic radiation (mobile phones/ WiFi / microwaves)

But virtually no studies
- No clear evidence either way.

EM radiation in animals:
- No clear immune effects in mature animals
- Some effects on newborn mice
- Effects in pregnancy: not known

Difficult to exclude effects of these more modern exposures
Medications in pregnancy and allergy risk

**Paracetamol:**
- increased asthma risk
- seen in multiple studies
- abnormal

**Anti-acid medications:**
- increased allergy
- increased asthma

**Antibiotics:**
- some evidence of increased asthma and allergy risk

Logical to avoid unnecessary medications in pregnancy
Role of fermented foods and probiotics

- Now >19 probiotic prevention studies (pregnancy and newborns)

- **Conflicting results:** depends on the strains and the population and lots of other factors

- **Summary (Cochrane Review)**
  - Some strains better (L. rhamnosus)
  - Effects only on eczema (not in all studies)
  - No reproducible effects of any other probiotics
  - No probiotics prevent other allergic diseases

Still no definitive benefits or recommendations

Need better strategies to define and restore microbial balance?
More refined modern diets (less fibre)
- Less favourable colonisation
- Less substrate for SCFA formation

Prebiotics (naturally in breast milk)
Promote favourable colonisation
Fermentation products \( \rightarrow \) anti-inflammatory

Prebiotic studies in newborns:
early promise in allergy prevention
Restoring n-3 PUFA status (fish oil)

N-3 PUFA
• Clear anti-inflammatory effects: many health benefits
• Deficient in western diets

Population studies (fish intake)
• Many studies showing allergy protection (esp. pregnancy)

Clinical trials (fish oil)
• Allergy protection (supplementation in pregnancy)

No official recommendations yet, but logical to restore n-3 PUFA (closer to traditional levels)
Reducing stress!!?

Stress affects immune function
• effects in pregnancy
• long-term effects in offspring
• some evidence in humans

Maternal stress and allergies
• higher IgE levels in newborns
• risk of wheeze and asthma

Infant stress levels
• cortisol levels indicate stress in babies, and higher allergy risk!

Logical to reduce stress for many health benefits
Restoring Vitamin D status?

Lifestyle changes: reduced sun exposure
- Declining vitamin D levels
- Rising rates of deficiency

Immune effects:
- Important for immune regulation

Implicated in allergy and asthma:
- Associations but no proven links
- Conflicting reports

Prevention studies (vitamin D in pregnancy): underway
In conclusion

• One of the greatest challenges of modern medicine is to learn how we can live in the new world we have created.

• We need:
  – A better understanding of our effects on the environment, as well as its effects on us!
  – To restore a form of ‘immune balance’ so that we are less prone to the growing number of modern diseases (NCDs) that result from inflammation and immune dysregulation.

• Restoring balance may improve many aspects of human health….

A healthy environment = healthy humans?
Book released September 2011
(all author proceeds donated to research)

• Paperback book
  - Can be ordered on-line
  - Publisher (UWAP)
  - Amazon / other on-line outlets

• E-Books

My hope: valuable, interesting resource for the public / patients / students / everyone!

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