How Early Nutrition Can Shape Gut Microbiota And Its Implications In The Autoimmunity Epidemics: The Lesson Learned From Celiac Disease

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The Yin and Yang Between Tolerance and Immune Response Leading To Immune-Mediated Diseases

- Human Genome
- Environmental Factors
- Microbiome
- Immune Response
- Clinic Outcome

Increased Gut Permeability
The Epidemics of Immune-Mediated Diseases In The Western Hemisphere: The Hygiene Hypothesis.
Autoimmunity Epidemics: Autism

Chart is updated from Autism Speaks: adds CDC 2012

Publication dates:
- 1 in 5000 (1975)
- 1 in 2500 (1985)
- 1 in 500 (1995)
- 1 in 250 (2001)
- 1 in 166 (2004)
- 1 in 150 (2007)
- 1 in 110 (2009)
- 1 in 88 (2012)
Food anaphylaxis in Italy

Ministry of Health, Health planning, essential levels of care and ethical principles of the system - Office VI.

Autoimmunity Epidemics: Celiac Disease

During the past 35 years the true prevalence of CD in USA doubled every 15 years.

The Hygiene Hypothesis Has Been Recently Questioned

Improved Hygiene In Some Developing Countries Was Not Paralleled by Increased Immune-Mediated Diseases
Microbiome Composition

- Vaginal Delivery
- Proper Nutrition
- No infections
- No Antibiotic treatments

- C section
- Inappropriate Nutrition
- Multiple infections
- Antibiotic treatments

Adequate Nutrition

Balanced Microbiome

Appropriate GALT Maturation

Tolerogenic Response to Food Antigens - State of Health

Genetic Predisposition

Pro-inflammatory Response to Food Antigens - CID

Inappropriate GALT Maturation

Dysbiosis
The human gut harbors $10^{11}$-$10^{12}$ bacteria per gram colonic content (>10$^{14}$ total bacteria)

- Total bacteria outnumber human cells 10:1
- Total bacterial genes outnumber human genes >150:1
- >10,000 different species of bacteria are resident in the human intestinal microbiota (400-500 per person)

Proof of Concept of Microbiome-Metabolome Analysis and Delayed Gluten Exposure on Celiac Disease Autoimmunity in Genetically At-Risk Infants

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\textbf{Abstract}

Celiac disease (CD) is a unique autoimmune disorder in which the genetic factors (DQ2/DQ8) and the environmental trigger (gluten) are known and necessary but not sufficient for its development. Other environmental components contributing to CD are poorly understood. Studies suggest that aspects of gluten intake might influence the risk of CD occurrence and timing of its onset, i.e., the amount and quality of ingested gluten, together with the pattern of infant feeding and the age at which gluten is introduced in the diet. In this study, we hypothesize that the intestinal microbiota as a whole rather than specific infections dictates the switch from tolerance to immune response in genetically susceptible individuals. Using a sample of infants genetically at risk of CD, we characterized the longitudinal changes in the microbial communities that colonize infants from birth to 24 months and the impact of two patterns of gluten introduction (early vs. late) on the gut microbiota and metabolome, and the switch from gluten tolerance to immune response, including onset of CD autoimmunity. We show that infants genetically susceptible to CD who are exposed to gluten early mount an immune
The Real Story of Our Genetic Complexity:
We Inherit two Parallel Genomes

Human Genome:
Inherited from both parents, stable, never change in its composition

Microbiome:
Inherited from the mother, extremely dynamic, changes from individual to individual and in the same individual over time
Higher Risk of Celiac Disease After Elective Cesarean Delivery

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Matched controls (%)</th>
<th>Celiac disease (%)</th>
<th>Odds ratio; 95% CI OR</th>
<th>P-value</th>
<th>Adjusted odds ratio; 95% CI AOR</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Cesarean delivery</td>
<td>5,766/53,887 (10.7)</td>
<td>1,299/11,749 (11.1)</td>
<td>1.04; 0.98-1.10</td>
<td>0.232</td>
<td>1.06; 0.99-1.13</td>
<td>0.074</td>
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<td>Number of participants</td>
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<tr>
<td>Emergency cesarean delivery †</td>
<td>2,136/41,699 (5.1)</td>
<td>444/8,827 (5.0)</td>
<td>0.99; 0.90-1.10</td>
<td>0.857</td>
<td>1.02; 0.92-1.13</td>
<td>0.749</td>
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<tr>
<td>Elective cesarean delivery †</td>
<td>2,125/41,688 (5.1)</td>
<td>508/8,891 (5.7)</td>
<td>1.11; 1.01-1.22</td>
<td>0.027</td>
<td>1.15; 1.04-1.26</td>
<td>0.005</td>
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</table>

Mårild et al Gastroenterology 2012;142(1):39
Infants intestinal microbiome is influenced by mode of delivery

Dominguez-Bello et al PNAS 2010;107(26):11971-5
Microbiome
(140-fold Human Genome)
Dynamic

Human Genome
(~30,000 genes)
Stable

Metabonome

Jazz

Pop

Classic

Clinical Outcome
Model for the Effects of Early Childhood Nutrition on Adult Health

Potential mechanisms:
methylation of genes,
acetylation of histones
? other epigenetic changes

Prenatal factors
- maternal nutrition, placental insufficiency

Birth
- ? similar mechanisms

Childhood factors
- malnutrition
- enteral infections
- inflammation
- poor weight gain
- stunting

Adult Health Risk factors
- Obesity
- Metabolic syndrome
- CVD T2DM

Adult Health Outcomes

Prenatal life — Early childhood — Adult life
Hypothesis

Combination of introduction of gluten into the diet and particular microbiota composition of infants genetically at risk for CD activates specific metabolic pathways that can contribute to the loss of tolerance to gluten and to the onset of autoimmunity, as reflected by specific metabolomic phenotypes.