



Science Supporting Exclusive Breastfeeding

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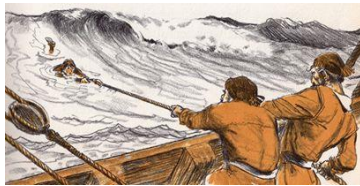
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- I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.



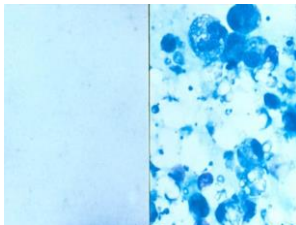
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What if the Breast Was Really an Immune System Gland?

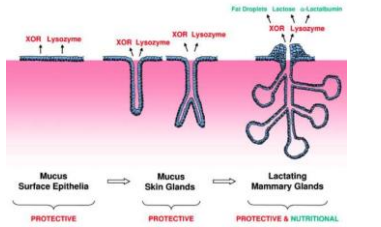


- In embryology, skin glands with protective infection-fighting effects are very common.
- The mammary gland evolved from a mucus-secreting skin gland, which would then help protect the skin of the newborn, even if the "newborn" was an egg.

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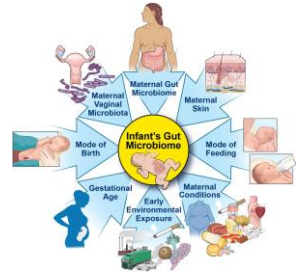
What if the Breast Was Really an Immune System Gland?



<http://capecchi.genetics.utah.edu/PDFs/150Vorbach.pdf>

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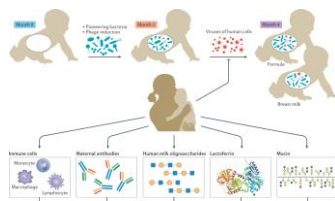
Microbiome



Kapourcheli 2020

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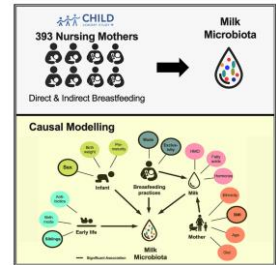
Human Virome



Liang 2021 Nature Reviews Microbiology

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Determinants of Gut Microbes



Shanahan J, Shanahan R, Shanahan R, Shanahan R, Shanahan R, et al. *Microbiome*. 2017;5(12):2111-2121.

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Determinants of Gut Microbes

- Mode of delivery: baby microbiota resembles maternal vagina, if delivery is vaginal, or skin, if delivery is via C-section
- Gestational age: preterm infants experience a number of challenges: antibiotic exposure, hospital stay, gut and immune immaturity

LeDoare et al. *Frontiers in Immunology* 2018

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Determinants of Gut Microbes

- Hill, et al. 2017
 - N=192 infants with different gestational ages, modes of delivery and feeding types from 1-24 weeks of age in Cork, Ireland, microbiota sampled at multiple time points.
- The influence of gestational age and mode of delivery on the early gut microbiota are apparent 24 weeks after birth
- The effects do decrease with age
- **Exclusive breastfeeding for more than 4 months impacts the microbiota of full-term C-section infants**

Hill CE, Lynch DB, Whelan K, Clavelles M, Murray IR, O'Shea CA, et al. *Evolution of gut microbiome composition from birth to 24 months in the BIFACTO cohort. *Microbiome*. 2017;5(1):1-11.*

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Determinants of Gut Microbes

- Breastmilk has hundreds of bacterial species
- Breastfed infants ingest up to 800,000 bacteria daily
- After the dose of bacteria at birth, breastmilk is the next source of bacteria seeding the infant gut
- During the first month of life, breastfed infants share about 30% of their stool microbes with mother's milk microbes

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Determinants of Gut Microbes

- Feeding method (at the breast versus milk pumped) was strongly associated with milk microbiota
 - Depletion of bifidobacteria
 - Enrichment of potential pathogens
- Also found evidence for the retrograde inoculation hypothesis- infant oral cavity influences milk microbiota

Al-Shahrri SS, Knox CL, Liley HL, et al. Breastmilk-Saliva Interactions Boost Innate Immunity by Regulating the Gut Microbiome in Early Infancy. *PLoS One*. 2015;10(9):e0135447.

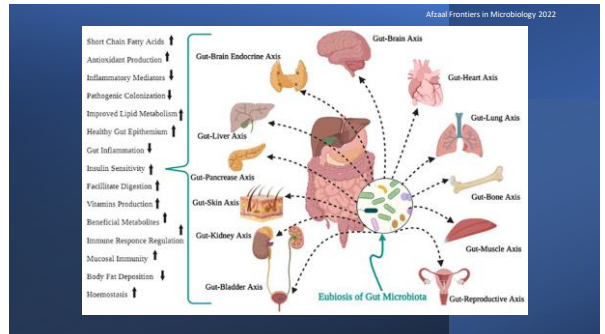
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Milk-Saliva Retrograde inoculation

- During breastfeeding, baby saliva reacts with breastmilk to produce reactive oxygen species, while simultaneously providing growth-promoting nucleotide precursors.
- This combination produces a potent combination of stimulatory and inhibitory metabolites that regulate early oral – and hence gut – microbiota.
- Represent unique biochemical synergism which boosts early innate immunity.

Al-Shahrri SS, Knox CL, Liley HL, et al. Breastmilk-Saliva Interactions Boost Innate Immunity by Regulating the Gut Microbiome

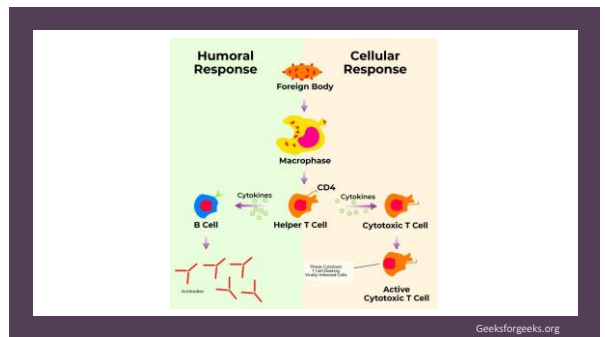
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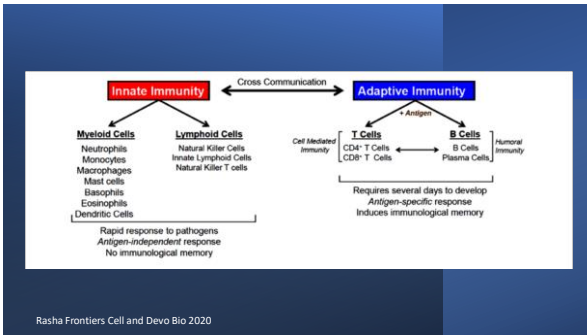
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Infection protection and anti-inflammation

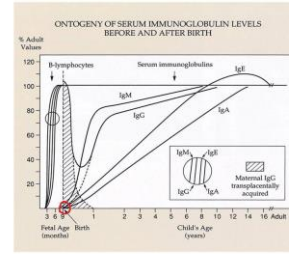
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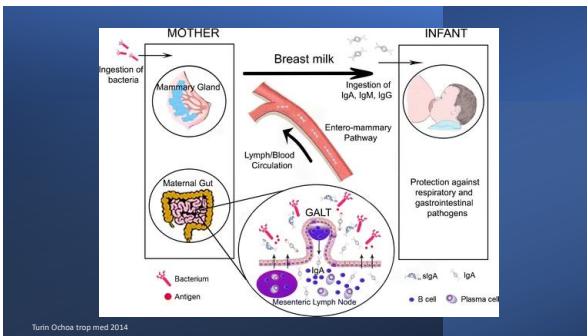
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Immunoglobulins in human milk

- IgA
 - Most abundant immunoglobulin in human milk 90%
 - Essential for conferring mucosal immunity
 - Originates in mammary gland
- IgM
 - About 8%
 - Arises from mammary gland
- IgG
 - About 2%
 - Originates in blood

Nicolisbar 2023

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IgG and IgA in human milk

- The highest concentration of IgG is in colostrum, decreases in the first month and stops with weaning
- IgG crosses the placenta
- In mothers with IgG against RSV, sIgG for RSV is found in breast milk
- RSV protection also comes from IgA antibodies to an RSV surface protein which inhibits viral replication

Mazur J Infect Dis 2019, Oddy J Asthma 2004

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Mazur J Infect Dis 2019, Oddy J Asthma 2004

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Preventing inflammation in the neonatal gut

Stopping the innate immune system

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Normal Innate Immune System Function

- Important for defense against infection because they engulf and kill microbes
- The price we pay is inflammation and tissue damage
- How does the newborn gut stay away from the damage potentially caused by phagocytes and the rest of the innate immune system?

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Lactoferrin and Covid

Interacts with heparin sulfate glycosaminoglycan cell receptors (HSPG) preventing attachment of SARS-CoV and host cells

Blocks spike protein and HSPG in an Angiotensin Converting Enzyme 2 (ACE2) receptor.

Vassilpoulou Frontiers in Immunology 2021

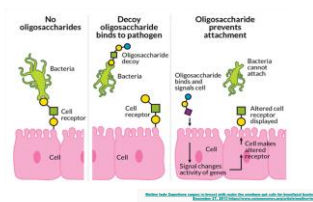
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Preventing inflammation: Prebiotics

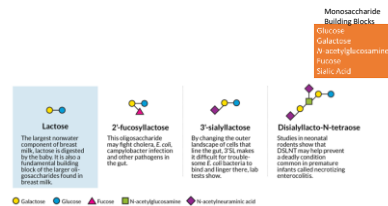
- They are non-digestible food components that beneficially affect the gut by providing food for the good bacteria that (hopefully) already inhabit it.
- In human milk, the most common prebiotics are oligosaccharides, which are also the third most common component of mature human milk.

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HMO as anti-adhesive antimicrobial



How do HMOs prevent infection? They block the attachment of cells to host cells (Barnes)



Bode L, et al. Adv Nutr 2012; 2:3(3):383S-391S

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Endocannabinoids & immunity

- Endocannabinoids have important effects on immune functions.
- Modulate T- and B-lymphocytes proliferation and apoptosis
- Macrophage-mediated killing of sensitized cells
- Inflammatory cytokine production
- Immune cell activation by inflammatory stimuli, chemotaxis and inflammatory cell migration

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Chrononutrition

Italianer Nutrients2020

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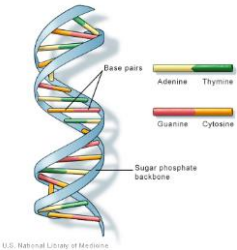
Human milk and the epigenome

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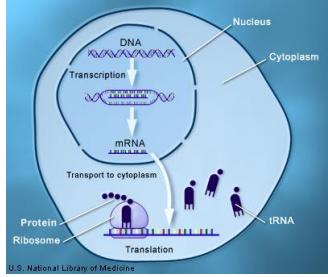
Review of genetics

For me, not you

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DNA to RNA to protein

That is how it goes, right?

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What is Epigenetics ?

- Genome = DNA
- Genes can switch phases
 - Active: directing protein production
 - Silent: no protein produced phases.
- Epigenome: Patterns of activation and silencing exist across all the genes in a cell.
- Changes in the epigenome do not change a gene's sequence, but rather its activity status.

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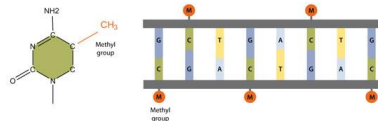
Molecular Basis of Epigenetics

- Two primary mechanisms:
 - DNA methylation**
 - Methylation of cytosine
 - MicroRNA**
- No alteration of the DNA sequence
- Changes gene expression

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DNA Methylation

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Choline

- Needed for the synthesis of the neurotransmitter acetylcholine, which is involved in memory and muscle control.
- Important for:
 - Synapse formation
 - Making cellular membranes
 - Methylation

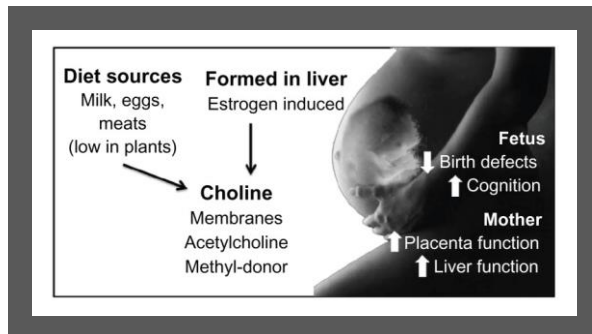


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Choline

- Choline is an important nutrient present in human milk, and it plays a crucial role in fetal and infant development.
- Choline plays a particularly important role in brain development, and researchers have shown that it can influence infant memory.
- Choline's effects on memory appear to occur as a synergistic effect with two other important nutrients, docosahexaenoic acid (DHA) and lutein.

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Choline

- Choline, DHA, and lutein often appear together in nature, such as in eggs and in human milk
- Independently, DHA, choline and lutein may not have effects
- There is synergy, where they have an effect when they are together
- The researchers found that higher choline levels with higher lutein levels were related to better recognition memory.
- Lutein works with choline to improve speed of processing in the infant brain
- DHA and choline work together, with high choline and high DHA associated with better recognition memory.

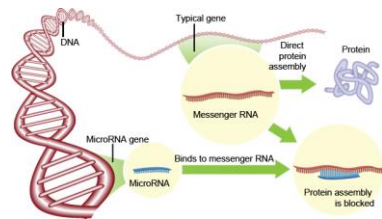
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Choline

- Diets in many low income countries and in approximately one-fourth of women in high income countries, like the United States, may be too low in choline content.
- Prenatal vitamin supplements do not contain an adequate source of choline.
- For women who do not eat foods containing milk, meat, eggs, or other choline-rich foods, a diet supplement should be considered.

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Steve Karp

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miRNA in Human milk

- Breastfed infants receive approximately **1.3 x 10⁷ copies/liter/day** of miRNA
- The highest concentration of miRNA of any body fluid
- Breast milk is a major epigenetic modulator of gene expression of the milk recipient
- MicroRNA is under the influence of hormones like insulin and prolactin
- MicroRNA can control DNA methylation

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microRNA in Human Milk

Epigenetic signals delivered to the infant through microRNA which can remove DNA methylation (and therefore increase protein)

Results in more protein for the baby that can help

- Metabolism
- Immune system
- Fat production
- Muscle production
- Bone growth

Melnik, Semenza 2017

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microRNA

- microRNA 148a most abundant: artificially increased in lactating cows because it increases milk volume
- It works by decreasing DNA methylation (it increases protein synthesis and increases gene expression)
- Works on the:
 - FOXP3 gene: helps with T cell activity and therefore decreases allergy risk
 - CCKBR gene: increasing food intake for growth
 - IGF1 gene: growth through fat metabolism

Melnik Clinical Endocrinology 2017

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Primary Prevention of Cow's Milk Sensitization and Food Allergy by Avoiding Supplementation With Cow's Milk Formula at Birth: A Randomized Clinical Trial

- Babies who received cow's milk-based formula in the first three days of life were at higher risk of cow milk protein allergy, including anaphylaxis, at age two.



Urashima JAMA peds 2019

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Infection protection

- Diarrhea
- Respiratory infections
- Otitis media
- Urinary tract infections
- Neonatal sepsis
- Coughing and wheezing
- Death

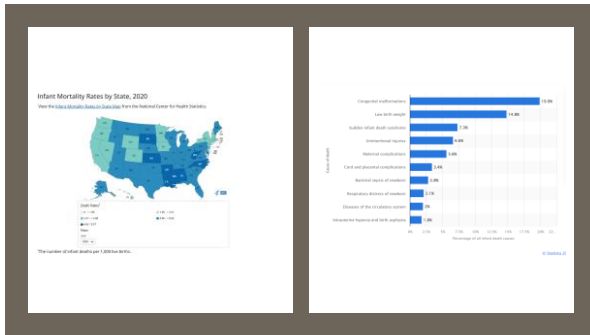
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Infant Mortality Rate



- Health and well being of a nation are reflected in Infant Mortality Rate
- Death before 1st birthday per 1000 live births
- US has a higher mortality rate than other high-income countries

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AAP Policy 2022

The AAP recommends exclusive breastfeeding for about 6 months, with complementary food introduction at about 6 months, and as mutually desired by mother and child, supports continued breastfeeding until 2 years or beyond.

**

Pediatricians need to provide information so that parents can make an informed feeding decision. The parental feeding decision should be fully supported, without pressure or guilt by any member of the health care team.

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Why 6 months?

- Fewer lower respiratory tract infections
- Less severe diarrhea
- Less otitis media
- Less obesity
- Less than 6 months is associated with abnormal microbiota
- Starting solids prior to 6 months offers no benefit to the breastfed child but does increase risk of infection and obesity

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