Epigentics and Breastfeeding – The Long-Term Impact of Breastmilk on Health

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Recent research on epigenetics, literally meaning above the gene, has led medical professionals to query about how the environment impacts the developing baby both in utero and throughout its lifetime. The genome is the genetic information inherited from one's parents, but the epigenome is what deciphers the genome for each cell throughout the body. This deciphering process is impacted by an individual's internal and external environment. The external environment can include nutrition, chemicals, toxins, etc. The internal environment would include neuropeptides (emotional molecules) and stress hormones. The environment changes the proteins in the body that help the epigenome translate DNA. This finding has increased awareness of the importance of nutrition on the epigenome. Studies now are finding that the changes in the epigenome can influence not only that individual but can be passed along to future progeny, sometimes multiple generations out. The first nutrition for a human outside the womb is breastmilk, and thus its epigenetic impact is particularly expansive. New research has expanded the field of epigenetics to include breastmilk and how it potentially changes the epigenome to affect the lifelong health of a baby.

Discovery of the Epigenome

For many years, it was believed that all the information the body ever needed to develop and grow person happened the moment of conception. There was the union that sparked a nucleus, a partnership of genetic information from the mother and father. It was thought that the baby's DNA contained all of the information it would ever need. The genetic destiny was thought to be sealed, and what would be - from the color her eyes to the manifesting of diseases - was all contained in the DNA strands coiled in her cells. Little did we know that there are ghosts of our ancestors lives present along the DNA. There are genetic memories of one's grandparents' and parents' stressors, emotions, and nutrition that change how DNA is expressed and our environments continue to change the epigenome throughout our lives.

We are all a unique and yet ancestrally connected conglomeration of genetic information that has been stored on our DNA and can potentially change throughout our lifetime. Our most critical developmental period, one that will forever impact how we grow, our personalities, and our long-term health, is the period from zero to three years old. This is the time when our DNA is most receptive to epigenetic tags

that mark our DNA and shift the way our organs develop and our propensity to certain diseases. To understand how this all works, it is important to see how the fledging field of epigenetics came to be.

In the early 1980s the project called the Human Genome Project was conceived. The goal was to literally identify and map all of the genes in human DNA. It was believed that if scientists could identify where all of our genes were and what they were linked to, there could have enormous strides in health care and disease research. The US government funded the 3 billion dollar project and early planning started in 1984, however it took until 1990 for the project to really gain momentum. Initial estimates suspected the project would take 15 years, but the actual genetic mapping research lasted from 1990 to 2003. Scientist from all over the world participated in this project – including but not limited to the U.S., Japan, the United Kingdom, France and Australia. The results are maintained in GenBank and are publicly available[2]. At the beginning of the project, scientists estimated that the human genome would contain about 100,000 genes. Surprisingly they found that actually the human genome was not as complex even as the genome of plants. The human genome only had about 20, 687 genes[3]. How could this be, how could human be less complex than a plant? Consider the mapping of the simple nematode or roundworm, *C. elegans* who has a sequenced of 20,470 protein-encoding genes, approximately the same as in the human genome. Humans have to be more complex genetically than a roundworm. Or do we?

This discovery led researcher to try and determine why it was that we could have so few genes and yet such a complex array of phenotypes and health outcomes. We essentially had a map with no key to understand how to read it. It was discovered that the exact same genes caused completely different diseases, such as in Prader Willi and Angelman syndromes. The same chromosomes caused different outcomes in different people. How could one unique gene have different outcome? It turns out that genes only make up about 2% of our genome, the rest is what used to be called junk DNA. In fact, the 98% "junk" is what makes us the unique and adaptable humans that we are. 20% of our junk DNA helps our genes turn on and off, known as regulatory sequences. An organization called ENCODE, the Encyclopedia of DNA Elements believes that 80% of our DNA is functional. The goal of ENCODE is to build a comprehensive parts list of functional elements in the human genome, including elements that act at the protein and RNA levels, and regulatory elements that control cells and circumstances in which a gene is active. An amazing part of our genome is the pseudogene, from our far away ancestry. These genes are no longer active but they are remnants of our past lives. They tell us what we used to be. It is as if we all carry along a detailed ancient family tree residing within our DNA. These pseudogenes contain information for furry pelts, tails, large jaws and vitamin C production. We no longer use these parts of our ancestral heritage, but the memories are there, like ghosts from our great, great, great grandmothers.

Francis Collins, the Director of the National Human Genome Research Institute said of the genome map, "It's a history book - a narrative of the journey of our species through time. It's a shop manual, with an incredibly detailed blueprint for building every human cell. And it's a transformative textbook of medicine, with insights that will give health care providers immense new powers to treat, prevent and cure disease." However, this shop manual only began to tell the story. The true fiction lies with the field of epigenetics and how our environments interact, change and leave permanent memory marks on our DNA.

What is the Epigenome?

There are several ways in which our genetic expression can be influenced. It seems as though every few months new epigenetic processes are discovered. Currently researchers have discovered the following epigenetics processes: methylation, acetylation, phosphorylation, ubiquitylation, and sumolyation. The most well known and studied are methylation and acetylation. Methylation occurs when a methyl group attaches to the cytosine base on the DNA strand. When this occurs, generally (though not always) it silences that gene. DNA is packaged with proteins into tiny collections called histones so that all the genetic information can fit into a dense bundle inside each cell. When acetyl groups attach to the histones, they loosen these bundles allowing more of the genetic information to be accessible for reading by proteins, thus more genes can be expressed. This is known as acetylation.

The Epigenome and the Mcirobiome

The most critical period of development, in terms of the epigenome, is the period of zero to age three for a human. The maternal environment during pregnancy and then the baby's first nutrition significantly impacts the epigenome. Many genes that can be influenced by the epigenome have to do with human metabolism, hormone production, and tissue sensitivity. We know that that many things can change the epigenome, including whether the baby was born via the vagina or cesarean section. The mode of delivery changes the bacteria that helps colonize the baby's microbiome, both inside and outside the body. The microbiome is the symbiotic and pathogenic microorganisms that live within our body space. The first seeding of the microbiome occurs in utero, but is strongly influenced during the delivery of the baby and with the first feedings. The microbiome, which interacts and influences the types of proteins and polysaccarides in the breastmilk, ultimately changes the methyl and acetyl groups affecting DNA. The proteins (associated with being breastmilk fed) ferment and create methyl groups in the infant. These methyls can turn on or off certain genes. Thus breastmilk itself is a gene switch.

One important bacteria in our microbiome is that of Bifidobacterium, which helps promote and support digestion. Babies who are fed artificial milk have a completely different bacterial profile and pH in their guts. When formula fed, a baby's gut changes from an acidic base of 5.1-5.4 to an alkaline base of 5.9-7.3. This change allows putrefying bacteria to take over and high levels of E coli, streptococci, clostridia, and bacteriodes to take over. This changes the fermentation process in

the gut and allows different levels of methyl and acetyl groups to be present, which change the epigenetic outcomes for those babies. Essentially, being breastfed leads to a healthy intestinal pH and microflora which leads to a healthy genomic expression, whereas being formula fed leads to a pathogenic intestinal flora leading to unhealthy epigenetic expression.

Epigenome Research

Research has now shown that the epigenome is not only modified and added to during fetal and early life but our epigenetic tags are passed down through generations. Animal research shows that some epigenetic tags stay in place up to 10 generations out. Researchers have been able to study epigenetic tags in humans up to 60 years out. The longest generational health data studying the epigenome involves the people who lived through the Dutch Hunger Winter and their subsequent generations. The Honger Winter lasted from the start of November 1944 to the late spring of 1945. It was a bitterly cold period in western Netherlands, which was under German control. There was a German blockade that prevented food deliveries to the Dutch population. The Dutch were trying to survive on only 30% of their normal daily calorie intake. People ate grass, tulip bulbs, and sawdust in a desperate effort to stay alive. More than 20,000 people died by the time food supplies were restored in May 1945. There were excellent records of the healthcare at that time and as such, we can see that the impact this famine had on the people of the Honger Winter and the babies conceived during that. Researchers have followed the subsequent generations and studied the epigenetic impact of this disaster. Depending on what stage of development the baby was in during the Honger Winter, certain epigenetic influences were triggered. The Honger Winter babies (and their subsequent offspring) were more like to have heart disease, diabetes, and suffer from a wide variety of brain related challenges such as bipolar disease and schizophrenia. These genetic tags have now effected several generations out.

A 2014 article by Verducci shows that many of the components in human milk can change gene expression in the newborn baby via breastfeeding. For example, lactoferrin affects immune disorders, prostaglandin J impacts obesity, Long Chained Polyunsaturated Fatty Acids and cholesterol impacts the risk of non-alcoholic fatty liver disease and cholesterol issues, and oligosaccharides influence Necrotizing Enterocolitis, immune disorders and obesity.

The epigenome is also responsible for priming the breast tissue between pregnancies. When a woman becomes pregnant her ductal and glandular tissue develops and proliferates. New research shows the mammary gland forms a long-term memory of pregnancy that primes it to respond to the hormonal changes that announce succeeding pregnancies (Dos Santos, 2014). The epigenetic memory lasts throughout the mother's reproductive years.

Another example of breastmilk effects on the epigenome was a recent study showing that breastfeeding was negatively associated with methylation of the leptin gene in very young children (Obermann-Borst, 2013). The hormone leptin,

produced by fat cells, is responsible for the regulation of food intake and the expression of energy regulating peptides. It is present in breast milk and when the baby consumes milk the hormone passes across the still "leaky gut" and enters the circulation, where it is biologically active. Milk leptin levels are inversely related to the rate of infant weight gain and infants who consumed mother's milk had higher leptin levels at 1 month old and were found to be thinner at 2 years of age. Higher leptin levels cause more satiety and less weight gain. When a baby is fed formula the gene that makes leptin gets dampened down. The more a baby breastfeeds, the less methylation or silencing of the leptin gene, meaning more leptin is produced.

Ozkan et al. proposed that breastfeeding from the same woman may lead to consanguinity, or kinship, between individuals even with no blood relation, and that children born of a marriage between two such individuals may then be at increased risk of certain genetic diseases as a result of this consanguinity (Oksan, 2012). It was one of the first papers to address whether wet nursing and milk sharing could potentially cause consanguinity? Why is this even a possibility? The researchers suggest that there are three reasons - exosomes, stem cells, and mRNA in breastmilk.

Human milk samples contain exosomes, which are tiny little particles that are excreted by every cell, and are believed to provide cell-to-cell communication. They contain everything necessary to change the behavior of neighboring cells, including microRNAs. The communication that is happening between cells via exosomes is genetically based. Therefore, if you are breastfeeding a child not your own or milk sharing, you are sending your genetic exosomes which influence the behavior in the cells of the baby receiving your milk.

Another way breastfeeding consanguinity can occur is via stem cells. Mothers and babies experience a sharing of stem cells during pregnancy and breastfeeding called microchimerism. The theory behind microchimerism is that these stem cells help provide immune protection for the mother long term, long enough to keep her around to care for the growing baby. During each breastfeeding a baby ingests thousands to millions of stem cells that are unique to the mother.

The Kosaka et al. (2010) study confirms the high levels of microRNAs in breastmilk in the first six months of lactation. A baby receives approximately 1.3×10^7 copies/liter/day of miR-181a. The research team believes these particular miRNA are present to help modulate the immune system. This study suggests that this is one additional way that humans can transfer genetic material other than through sexual reproduction.

The epigenetic changes are not just related to the breastmilk itself, but also the act of breastfeeding itself. The babies of mother rats who lick, groom and arch their backs during breastfeeding to allow for more skin to skin and access to milk have a more moderate stress response. Additionally the babies who have higher touch mothers have epigenetic changes that influence the hippocampus development and release of glucocorticoid receptor expression (Weaver, 2004). How we touch, hold,

and practice skin to skin with our babies can change the epigenome, as well. Weinstock (2015) showed that when mother rats were stressed out during pregnancy, their babies had damage to the HPA axis in the brain, as well as increased anxiety. If the prenatally stressed babies were then fostered and nurses by non-stressed rats, their HPA axis was repaired and their anxiety decreased.

In Closing

Knowing how important a baby's first food is to the health of the baby long term, it is vital that healthcare professionals start to talk to families about all of their options for accessing breastmilk in the event that a mother cannot breastmilk or provide breastmilk to her baby. All mothers should be educated on the availability of breastmilk from human milk banks. In France, one can access donor milk though the European Milk Bank Association, EMBA. Additionally, it is also important to share information with mothers who cannot access donor human milk on share milk systems. They should be educated on how to access, as well as the risks and potential benefit of share milk. Every mother has a right to make a decision to have her baby completely human milk fed if she so chooses, especially considering this new information regarding the importance of human milk and the epigenome.

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Professional Organizations and Projects

- list-behavior=unordered prefix-word= mark-type=disc
- DNA Methylation Society (international) http://www.dnamethsoc.com/main.htm
- Epigenome Network of Excellence (Europe) http://www.epigenome-noe.net
- Human Epigenome Project (Europe) http://www.epigenome.org

Journal

Epigenetics
http://www.landesbioscience.com/journals/epigenetics/

DNA Methylation Database

http://www.methdb.de/front.html

Imprinted Gene Databases

- list-behavior=unordered prefix-word= mark-type=disc
- http://igc.otago.ac.nz/home.html
- http://www.geneimprint.com/databases/?c=clist

http://www.mgu.har.mrc.ac.uk/research/imprinting/