



SPLASH! milk science update DECEMBER 2013 issue

This month's issue addresses the controversy surrounding pregnant moms drinking cow's milk, how milk composition changes in response to an infant feeding, the breakthrough research regarding the genetic controls behind milk production, and the discovery of a gene that influences the level of protein in cow's milk. Enjoy!

Cow's Milk for Breastfeeding Moms

- **Breastfeeding babies are less likely to develop cow's milk allergy when their mothers drink cow's milk.**
- **Mothers who drink cow's milk have higher levels of secretory IgA in their breastmilk.**
- **A cell culture study shows that "high sIgA" breastmilk blocks uptake of an undigested cow's milk protein by intestinal cells.**
- **A randomized controlled trial is needed to verify the linkage between dairy consumption and breastmilk sIgA, and subsequent protection of breastfeeding babies.**
- **In the meantime, breastfeeding mothers should drink cow's milk.**

New mothers are often given a mile-long list of do's and don'ts, dished out by doctors, families, friends, and even strangers. Somewhere along the way, eating certain foods got put on the "don't" list. Typical scenario: sleepy new mother eats peanut butter sandwich, mother's friend reacts as if eating peanuts is akin to balancing one's child over the food allergy abyss.

Cow's milk allergy is often in the crosshairs of such well-meaning, but misguided, allergen avoiders. People commonly believe that potentially allergenic foods should be avoided during pregnancy and lactation to help prevent the development of those allergies in their kids. Let us put that myth to rest. A 2008 report in *Pediatrics*, the official journal of the American Academy of Pediatrics, concluded there is insufficient evidence to recommend that women avoid allergenic foods, such as milk, during pregnancy or lactation for the purpose of preventing allergic disease (1). Furthermore, avoidance of foods like milk puts mothers at risk for nutrient deficiencies.

In fact, avoidance of cow's milk by a breastfeeding mother may even *increase* the infant's chance of developing cow's milk allergy. In a new study appearing in *Clinical & Experimental Allergy*, researchers reveal evidence for why breastfeeding babies are less likely to develop cow's milk allergy when their mothers drink cow's milk (2). When mothers consume cow's milk, they have greater amounts of secretory IgA in their breastmilk. Secretory IgA is a type of antibody that lines the infant's intestinal tract to form a barrier capable of neutralizing threats that come down the pipe. Secretory IgA (sIgA) is like a bouncer at the local club, letting in the good clientele (nutrients) while keeping out the troublemakers (pathogens).

Given that milk-avoiding mothers had lower levels of sIgA in their breastmilk (2) and previous studies had also associated low breastmilk sIgA with development of cow's milk allergy (3,4), the researchers next looked for a reason why breastmilk sIgA might prevent allergy (2). Using intestinal cells in a petri dish, they tested whether an allergenic milk protein unique to cow's milk (beta-lactoglobulin) could pass through intestinal cells in the presence of "low sIgA" breastmilk and "high sIgA" breastmilk. The higher the sIgA, the less beta-lactoglobulin could get through the cells, meaning.... Importantly, sIgA levels had no effect on a control (dextran), suggesting the blocking was specific. In the context of a baby, this would mean that less undigested beta-lactoglobulin is absorbed across intestinal cells and, therefore, there would be a lower chance of the baby developing an allergic reaction to beta-lactoglobulin. This is probably not the end of the story, as other immunoregulatory mechanisms are likely at work.



Although the study impressively followed 145 mother-infant pairs (2), it was not a randomized controlled trial, so there is always the chance that mothers who chose to avoid cow's milk may have other aspects of their breastmilk that predispose their infants to allergy, not to mention the genetic linkage of mother and child. Along those lines, other researchers in another recent study investigated whether mothers with allergies have an altered composition of breastmilk (5). They found that, compared with allergy-free mothers, mothers with allergies had lower concentrations of sIgA in their breastmilk. Were the mothers with allergies avoiding cow's milk? Unfortunately, maternal food intake was not reported. One could safely hypothesize, though, that the mothers with allergies avoided cow's milk, leading to their lower concentrations of sIgA. Again, a randomized controlled trial is sorely needed to determine unequivocally whether low breastmilk sIgA results from maternal avoidance of cow's milk.

In the meantime, the take-home message is this: breastfeeding mothers, who are not allergic to milk, should drink cow's milk. There is no evidence to discourage it and some evidence that it may protect the nursing infant. Dear Mothers: when friends freak out, keep calm, drink on.

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Breastmilk Composition is Dynamic: Infant Feeds, Mother Responds

- **Milk composition is not constant but changes in the short term in response to milk removal by the infant.**
- **The highest levels of lipids and cells in breastmilk occur 30 minutes after a good feed.**
- **Changes in gene expression stimulated by milk removal may facilitate secretion of lipids and active migration of cells into breastmilk.**
- **The dynamic changes in breastmilk composition that are driven by feeding provide a basis for standardization of sampling for lactation studies.**
- **The 30-minute maximum of lipid and cell content of breastmilk generates new avenues for optimisation of infant feeding, especially for compromised infants.**

Unlike formula, breastmilk composition is dynamic, responding to milk removal that occurs during breastfeeding. This plasticity of breastmilk composition may be key to early infant growth and programming of development. An exciting new study demonstrates how removal of milk by the infant stimulates changes not only in the lipid composition but also the cellular components of breastmilk. This knowledge now sets the basis for new clinical interventions aimed at improving health outcomes of compromised infants, such as those born prematurely.

The milk of each species is unique

Breastmilk is so much more than nutrition, containing molecules that protect the infant as well as epigenetic modulators that program development^{1,2}. The milk of each mammalian species has a unique composition that evolved over millions of years to suit the needs of the young for which it is intended^{1,3}. This is reflected in the large variations in both lactation strategies and milk composition among different mammalian species³, as well as in pathologies that often result from the consumption of milk of one species by another^{4,5}. In addition to interspecies variations, milk composition

varies within species⁶. For example, maternal diet is known to influence breastmilk fatty acid composition⁷. Even more intriguing, breastmilk composition varies within an individual mother, with these constant changes potentially facilitating important physiological functions.

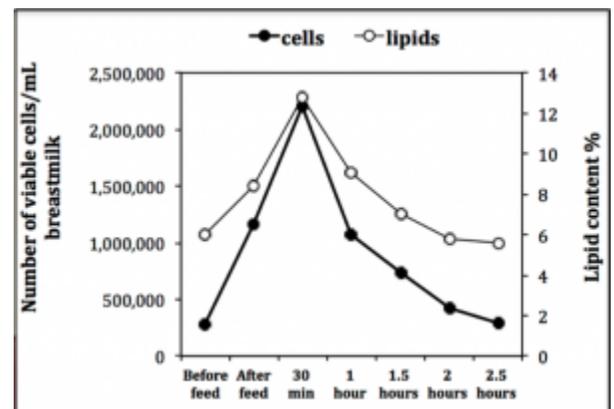
Milk composition is constantly changing

The fascinating fact that milk composition changes constantly during periods as short as a breastfeed^{8,9} and as long as the entire lactation period^{2,10,11} gives rise to speculation of whether these changes benefit the infant or simply reflect physiological changes associated with the synthesis of milk. New studies now reveal that these changes in milk composition are more extensive than once thought. We have known that breastmilk lipid content fluctuates throughout the day in response to infant feeding such that prior to a feed, when the breast is fuller, the milk has lower lipid content than immediately after a feed when the breast is emptier^{12,13}. However, empirical evidence from our laboratory had indicated that breastmilk expressed some time after the end of a feed often had higher lipid content than the breastmilk obtained immediately post-feed. This seemed to be related to the milk volume removed during the feed, with larger feeds showing a more marked response. Naturally, we were curious to investigate this further.

More breastmilk = more fat = more cells

Breastfeeding mothers from different stages of lactation were recruited and asked to provide a small breastmilk sample prior the first morning feed, immediately after the feed, and then at 30-minute intervals for the next three hours after the feed¹⁴. We examined how breastmilk lipid content changed during this period and coupled this with measurements of the cell and protein contents of breastmilk. The aim was to elucidate how the degree of breast fullness affected breastmilk composition.

All examined feeds were of more than 52 ml of milk. In all mother-infant dyads, the lipid and cell contents immediately after the feed were higher compared to pre-feeding, but the highest lipid content of breastmilk was seen 30 minutes post-feed, after which it gradually dropped as the breast synthesized milk and refilled. Exactly the same response was seen for breastmilk cell content. This very close association between the cell and lipid content of milk and the corresponding changes in response to breast emptying was indeed remarkable! The increase of lipid and cell contents at 30 minutes post-feeding was several fold higher compared to the pre-feed values¹⁴. Interestingly, the rate decrease of lipid and cell content after the 30-minute maximum was different between mothers, something that can be used to determine individual rates of milk synthesis.



of

This new study now clearly demonstrates that the degree of fullness of the breast is closely associated with breastmilk lipid and cell contents across different times of the day and lactation stages, potentially reflecting a dependence of breastmilk content on feeding history and milk synthesis rates of the breast. But how is this effect mediated?

And the mechanism?

The previous observations of the increase in milk lipid content immediately after a feed had led to two hypotheses to explain this phenomenon. The filtration theory proposes that fat globules cluster and adhere to the walls of the alveoli and ducts and are then filtered out as milk is gradually removed during breastfeeding or breastmilk expression¹⁵. The adsorption theory suggests that fat globules remain adsorbed to the membranes of the alveolar cells and get displaced only when the gland is nearly empty¹⁶⁻¹⁸.

Given that milk cells also form clusters like milk lipids^{19,20}, it is possible that these theories may also hold for the increase in breastmilk cell content immediately after a feed. However, the 30 minute post-feeding peak of breastmilk lipid and cell contents can only be explained by these theories if one assumes that milk fat globule and cell clusters remaining attached to the epithelium after feeding are washed off into the milk within those first 30 minutes after a feed¹⁴.

Both of these theories base their mechanistic explanations solely on the physicochemical phenomenon of milk removal from the breast. Perhaps a more likely explanation could involve both the physical process of milk removal from the mammary gland and the biology of milk synthesis. In the current study, breastmilk protein content did not respond to

feeding in a systematic manner; however, there were strong inter-individual variations in protein responses to feeding, from no change to increases at various time points after a feed. Given that protein is soluble in milk, these protein content changes cannot be explained by the physicochemical phenomena proposed by the adsorption or filtration theories¹⁴.

Consequently, a biological, rather than physical, response of mammary cells to milk removal is an attractive alternative mechanism to explain the changes observed in breastmilk composition in response to feeding. In this context, we have previously shown that gene expression in the mammary gland changes in response to feeding²¹, a finding consistent with recent studies in the dairy cow showing that milking induces changes in gene expression in the mammary gland^{22, 23}. These changes in gene expression are reflected not only in milk cell content but also cellular composition^{14, 23} and may be related to the changes in lipid content post-feeding.

Standardization of lactation studies – Explanation of previous variability

Cell and lipid content of breastmilk in the literature varies wildly among women. Although it is established that variation in breastmilk lipid content is related to breast fullness, our new findings that the latter is also associated with breastmilk cell content help illuminate the reported variation, especially given the lack of standardization of breast fullness during sample collection in previous studies. It is now imperative that breastmilk composition studies standardize sampling protocols taking into account breast fullness.

Furthermore, these changes in breastmilk composition with feeding may also explain previous observations of diurnal changes in milk composition. Indeed, ignoring the effects of milk removal on breastmilk composition make the conclusions of studies examining diurnal variations in breastmilk composition less robust. At the same time, the intra-individual variation observed in breastmilk cell, lipid and protein content now calls for more rigorous sampling as it is evident that one feed is not representative of an individual¹⁴. This is particularly important when it comes to investigating the functional significance of the dynamic nature of breastmilk composition.

Physiological significance for the breastfed infant

How does the variation in milk composition affect the infant? Intra-species variations are buffered by both the mobilization of maternal somatic nutrient stores and the changing needs of the infant, resulting in personalized breastmilk that reflects the balance between maternal diet, metabolism, transport and secretion, and meets the growth and developmental requirements of the term infant during the early postnatal period²⁴. Thus, in addition to understanding the mechanisms mediating feeding-induced changes in breastmilk composition, it is important to elucidate the physiological significance of these changes for the breastfed infant. The post-feed increase in milk lipids is implicated in short-term appetite control as well as the development of the infant's appetite control system, although these require more rigorous study^{14, 24}. However, the role of milk cells for the infant is not yet clear. It was recently established that breastmilk contains a cellular hierarchy, from pluripotent stem cells to progenitor cells to more differentiated mammary cells^{25, 26}. Investigations of the function and properties of these cells are ongoing in our laboratory, and the changing breastmilk cell composition in response to feeding may provide appropriate time points for the harvesting of the different cell populations for specific research and application purposes^{21, 27}.

Implications for the preterm infant

Although term milk meets the growth and nutritional requirements of the term infant, preterm milk does not meet the requirements of the preterm infant to grow at a rate equivalent to intrauterine growth. This has led to preterm milk fortification to promote infant growth and survival. The unexpected finding of increased lipid and cellular content 30 minutes post-feeding opens up new avenues for optimization of the nutritional care provided to the preterm infant. Clinically providing selective portions of expressed breastmilk higher in lipids and live cells has the potential to provide beneficial outcomes in regard to the growth and development as well as health of preterm infants.

Outlook

Quite simply, it is astounding that the mammary gland has the unique ability to produce milk that dynamically responds to changing infant needs and the interplay between the mother and the infant during breastfeeding. Our work highlights the unique dynamic composition of breastmilk that contains live components such as maternal cells, which may provide valuable developmental signals to the growing infant, which are absent in formula. Thus, these new findings urge us to improve women's experiences of lactation in order to extend the period of breastfeeding, with the goal of ensuring maximal health benefits to both the mother and infant.

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Milk-On, Milk-Off

- **The mammary gland has a switch to turn lactation on and off.**
- **Mammary genes are controlled in groups, and some genes exist in “neighborhoods.”**
- **These gene neighborhoods are consistent across various tissue types.**
- **Most gene neighborhoods are silenced during lactation.**
- **Genes uniquely turned “on” in the mammary gland are isolated from neighbors.**
- **There may be advantages in grouping genes that need to be silenced during lactation.**
- **Scientists now have a better understanding of how milk production is controlled at the molecular level.**



If we could travel along a chromosome, we would find genes arranged in clusters. Sometimes the genes within the cluster have some shared function, but other times they seem to be randomly organized. Lactation biologists have often wondered how the mammary gland turns on lactation and keeps the milk flowing when needed. In a recent study by Danielle Lemay and her colleagues¹, they investigated the potential role of gene cluster arrangement and coordinated control of lactation. Interestingly, they found that the clusters of lactation genes may be more relevant to which genes are turned off during lactation rather than which are turned on.

The power of global databases and Internet connectivity means that a very large amount of mammary gland and lactation-associated data are now available from laboratories around the world. These data allow researchers to openly collaborate and extend analyses. Lemay et al. downloaded a series of functional lactation cycle data to perform computer-based analyses on what are referred to as gene neighborhoods and functional clustering.

First, the research required the development of a new computer tool or program to extract and analyze the data in a customized way. The tool, named G-NEST, automated the analysis of genes that were turned on during lactation and their location in the genome. When each gene was compared to every other gene in the analysis, the distance between them was a crucial factor in whether they were both turned on at the same time. There were clear neighborhoods of genes, ranging in size from two to five neighbors, that followed the same on/off pattern. This confirmed a fundamental principle and supported the view that genes are controlled in groups. However, when the researchers looked at the way in which genes that are active in the mammary gland are arranged and compared that arrangement to other tissues, they found that very similar patterns were present across those tissues and were not specific to the mammary gland. So the very specific biological functions of the mammary gland are not reflected in the way that the genes are organized.

Next, the investigators generated a set of data that identified marks on the genes and surrounding regions that reflect whether the genes in that region are active or not. They also developed a ratio that allowed them to calculate which of these marked regions were in fact active and which ones were silent. Again they identified regions that were clearly marked in the mammary gland, but these regions were similar to those in other tissues. Importantly, what the analysis showed was that the very large majority of regions were switched off during lactation.

Once lactation begins and moves past the colostrum stage, the purpose of the lactating mammary gland is to produce milk that is reasonably consistent in composition, with protein components largely dominated by caseins and a few other proteins. This provides a very important nutritional basis for the newborn. It seems the findings of the study by Lemay et al. reflected this dominance of a few gene products; that is, most genes were turned off and the cell machinery focused on producing lots of a few proteins, as well as some lipids and carbohydrates. The study also showed that active gene neighbors were unlikely to regulate the biology of the mammary gland. In fact, the more powerful regulatory genes were found outside of neighborhoods.

This research provided another piece of the puzzle for lactation biologists. It is essential in trying to understand what controls lactation, and in some cases the failure of sufficient milk production, that we appreciate the importance of gene modifications. These modifications can arise from the environmental, nutritional or health status in the womb, or early in life, and can have a long-term impact on how the mammary gland regulates milk production. This paper highlights that what is turned off in the mammary gland during lactation may be a major driver of why gene neighborhoods are needed. Less is more when it comes to milk!

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Genes for More Proteinaceous Milk

- **Selective breeding of livestock based on genomics, rather than physical characteristics, is becoming more common as genes responsible for variation in economically important traits are uncovered.**
- **One such gene is RNASE5, which occurs in various forms.**
- **RNASE5 and its regulatory genes appear to influence the level of protein in cow's milk. It follows that cattle could now be bred to maximize this feature.**



The world of cattle breeding is one of extremes. With the help of the international postal service, humans have skewed the genetics of the rich world's cattle herds so much that even the most polygynous elephant seal couldn't keep up. Just two bulls, 'Pawnee Farm Arlinda Chief' (Chief, born in 1962) and his son, 'Walkway Chief Mark' (Mark, born 1978), [have no fewer than 60,000 daughters](#) between them in Australia, plus countless others elsewhere. This is a blessing for detectives of milk genetics for it makes the task of correlating milk output with complex genomic features much cheaper than it would otherwise be.

Ben Hayes of the Department of Primary Industries in Bundoora, Australia, and his associates are among the top milk genetics detectives out there. Last year they published a paper¹ in the journal *PNAS* describing the sequences of Chief's and Mark's genomes and identifying a series of genes that have been under strong (artificial) selection pressure. These genes are therefore likely to have a hand in important traits for breeding a profitable herd, such as high milk-production (in females only, obviously), high fertility, and resistance to various diseases.

In a more recent paper², Hayes and his colleagues home in on a series of genes that directly alter milk composition in cows. They focus on one gene in particular, called RNASE5, and on almost a dozen other genes that influence how RNASE5 is regulated.

Surprisingly little is known about the biochemical processes that determine why the proportions of various fats and proteins in cows differ in their milk. This is surprising given the economic incentive to find the answers. Scientists reckon 23% of the variation in milk protein yield is inherited. And this in turn implies that once the main genes that account for this 23% are identified, breeding programs designed on the basis of genetic features could lead to cows with especially high-protein milk.

RNASE5 encodes a protein called angiogenin, which has a long list of known biological roles. It is produced in many different cell types and seems to partially regulate ribosomal RNA synthesis, meaning it acts as a potential bottleneck in many kinds of cells' protein production lines. Going into the recent study, no one knew whether angiogenin has a role in lactation. What was known, however, was that angiogenin occurs in slightly different forms because RNASE5 does as well. Hayes's hypothesis is that these different forms of RNASE5 explain variation in the protein levels found in cow's milk.

Indeed, the results of the study demonstrate that RNASE5 does alter milk protein levels—and that different versions of the RNASE5 gene, or perhaps of the genes that regulate this gene, explain some of this variation. So, at least in theory, farmers could henceforth purchase bull sperm according to how likely the resulting progeny are to inherit genes for milk with high protein levels. Welcome to the future of farming. Welcome to a future where genetic selection nudges out selection reliant upon visible traits and educated guesswork.

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Funding provided by California Dairy Research Foundation and the International Milk Genomics Consortium