



SPLASH! milk science update JUNE 2014 issue

This month's issue features articles about prevention of tumor growth in mice by fermented milk, the influence of celiac disease on breast milk composition, fighting disease and health enhancement by bovine lactoferrin. Enjoy!

Fermented Milk Prevents Tumor Growth in Mice

- A major strategy in fighting cancer is to activate the host immune system.
- This study measured growth of breast tumors in mice fed fermented or unfermented milk.
- Fifty percent of mice fed milk fermented with *Lactobacillus casei* had no tumor growth.
- The authors concluded that the effect was due to restricted tumor blood supply and immunomodulation.



One of the most promising recent developments for fighting cancer is the introduction of treatments based on activating the immune system of the patient to fight the disease (1). A recent report by Aragon et al (2) reported that laboratory mice fed fermented milk had modulated immune responses and slowed tumor growth.

Immune systems are constructed to recognize what is a normal cell and what is abnormal. This is an active process that involves continued surveillance of all tissues looking for signals from affected cells. Under normal circumstances, the immune system does a thorough job, and all cells that flag a problem are detected and carefully removed. Some viruses have evolved ways to evade detection by lowering or removing the flags. A

similar thing happens with cancer cells, and they multiply and form tumors that remain undetected by the immune system.

Tumor growth also requires an increase in blood supply (3, 4). In fact, some of the latest anti-cancer drugs target tumor blood supply to cut off the nutrient source required for all the energy needed for continued rapid growth (5). The molecular and cellular events that lead to formation of cancers are complex and understanding them often requires that they be studied in animals. Cancer biologists have developed many cancer cell lines in the laboratory, and have used these to study the characteristics of tumor growth and for development of new treatments. The mouse mammary cancer cell line 4T-1 is one of these lines. The features of this cell line are equivalent to an advanced stage of breast cancer cells in humans (6, 7).

Blood supply is essential to tumor growth. The tumor promotes the production of new blood vessels that become an integrated part of the tumor and keep the multiplying cells alive. When Aragon et al (2) removed the tumors, they looked closely at how many blood vessels were present. They reported that tumors from mice that received the probiotic supplement had an average level of blood vessels that was approximately 10% of the other groups. The authors concluded that the effect was due to restricted tumor blood supply as a result of modulation of the immune response and reduced inflammation.

The differences in tumor growth in this study are intriguing, albeit observed in a relatively small number of mice. There were clear differences in the treated group, but as with many studies, providing a mechanistic account for such multifarious phenomena in which there is an apparent impact of an oral supplement on a distant and complex biological process is a major challenge. The burden of proof falls back to all scientists working in these areas. As with all research, we don't expect paradigm shifts from any one study, but rather from the weight of evidence emerging from multiple, reproducible studies. We also need to develop more sophisticated tools and interpretations of biomarkers in the study of complex events, like those we encounter in cancer biology and immunology. This is where advances in genome sciences will take us in the very near future.

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Celiac Disease Influences Breast Milk Composition

- Celiac disease is an autoimmune condition where the body's immune system reacts to dietary gluten by damaging the lining of the small intestine.
- Milk from mothers with celiac disease has lower concentrations of protective immune factors, including secretory IgA and probiotic bacteria, compared with healthy controls.
- Although breastfeeding may reduce the risk of subsequent celiac disease development, milk from mothers with celiac disease may not provide sufficient quantities of these protective factors.
- More longitudinal studies are needed to fully understand how variation in breast milk immune components and probiotic concentration influences the development of celiac disease and other autoimmune conditions later in life.

Nearly 1% of Americans suffer from the autoimmune disorder called celiac disease. For these people, the digestion of foods containing gluten (a protein found in wheat, barley and rye) causes the immune system to attack the lining of their small intestine, resulting in inflammation that prevents absorption of nutrients. The intestinal damage from celiac disease can lead to anemia, osteoporosis and weight loss. But can it also influence breast milk composition? A new study reports for the first time that mothers with celiac disease produce milk with lower concentrations of protective factors, including antibodies and probiotic bacteria (1).

Guts, Immunity and Milk



If celiac disease affects the small intestine, why would it affect breast milk composition? Although milk is produced by the mammary gland, some milk components may have their origins in the maternal gut. In fact, in a lactating female, the mammary gland develops a special relationship with the lymphatic (immune) system in the gut (called GALT, for gut associated lymphoid tissue); take, for example, secretory immunoglobulin A (sIgA), the predominant antibody in human milk. Milk sIgA molecules are derived from maternal IgA antibodies directed against pathogens that the mother encountered in her own digestive tract. Damage to the villi that line the small intestine in mothers with celiac disease could influence maternal IgA production and, subsequently, the sIgA concentration in breast milk.

Another important consideration is the intimate connection between the maternal immune system and milk immune components. Celiac disease, like other autoimmune conditions, is associated with an inflammatory immune response. As a result, the concentration of immune factors associated with inflammation, such as the cell signaling proteins interleukin 12 (IL-12) and transforming growth factor-beta 1 (TGF- β 1), may be altered in maternal serum and in breast milk.

Taking these factors into account, Olivares et al (1) collected breast milk samples from mothers with celiac disease and healthy controls to compare the concentrations of sIgA, cytokines involved with the inflammatory response (including IL-12 and TGF- β 1), as well as DNA from probiotic bacteria.

An important component of the investigators' study design is their inclusion criteria for the celiac disease group. They only collected milk from celiac disease mothers that had consumed a gluten-free diet for at least two years and had no reported symptoms of the disease at the time of the study. By doing so, they were able to rule out the possible effects of an active inflammatory response in the maternal gut tissue (or even malnourishment) as a cause for the differences they detected in milk composition between the celiac disease and control groups.

Keeping in mind the small sample size (24 mothers total, 12 in each group), Olivares et al (1) made some exciting observations. First, milk from mothers with celiac disease was significantly lower in the concentrations of sIgA, IL-12 and TGF- β 1. Moreover, their milk had less DNA from gut-derived probiotic bacteria, including *Bifidobacterium* species and *Bacteroides fragilis*, although these differences were not as pronounced as those for sIgA and cytokines. Lower levels of *Bifidobacterium* species in the gut also were reported in milk from mothers with allergies (2), suggesting a relationship between the maternal immune system's response to "false alarms" and milk probiotic bacteria. On the other hand, higher concentrations of milk sIgA were associated with maternal infection, psychological stress, and heightened microbial exposure (3, 4). Olivares et al's (1) finding of reduced concentrations of sIgA in celiac mothers suggests that autoimmunity, previous inflammation in the maternal gut, or a combination of both factors may have suppressed maternal IgA (and cytokine) production. This issue could have been more fully addressed had the investigators measured sIgA or cytokine levels in serum from the mothers to compare with levels in their milk. For example, although the mothers with celiac disease reported no active symptoms, they may still have had a pro-inflammatory immune profile compared with the control group.

Breastfeeding and Celiac Disease: It's Complicated

Olivares et al (1) provide the first evidence that celiac disease influences human milk composition. That alone is a significant contribution to the study of human lactation. But their study may make its largest impact by contributing to the debate over whether or not breastfeeding provides a protective effect against the development of celiac disease. Despite numerous studies identifying a reduced risk of developing celiac disease associated with breastfeeding (5–7), others (8) failed to identify any protective effects.

At the heart of the debate is whether breastfeeding at the time of gluten introduction to the infant's diet delays the onset of celiac disease, or even prevents the development of the disease in infants with a genetic predisposition. Olivares et al (1) believe that their findings can help provide much needed resolution. Each of the milk factors they found to be significantly lower in celiac disease mothers has been implicated as potential protective components against the development of celiac disease, other autoimmune diseases (e.g. Crohn's disease) and allergies. TGF- β 1 is believed to help regulate the infant's immune response to food antigens (9), sIgA is critical in regulating the mucosal immunity in the infant's gut (10) and imbalances in probiotic bacteria are connected to the development of autoimmune diseases (1, 11). Taken together, these components are intimately involved in the development of the infant's immune response to environmental antigens such as gluten.

The majority of studies investigating the relationship between breastfeeding and celiac disease are retrospective in design; study participants are asked to recall information about the duration of breastfeeding and age at which gluten was first introduced into the diet. As a result, breast milk composition has never been considered as a possible confounding variable.

At this point, we know too little about the consequences of variation in milk immune components on infant outcomes to say definitively that milk composition could be a confounding variable in the development of celiac disease. For example, although mothers with celiac disease produce lower concentrations of sIgA and TGF- β 1 than mothers without the disease, how do we know whether these levels are insufficient to promote oral tolerance of food antigens? Despite these gaps in our knowledge, the results of Olivares et al's (1) study illustrate just how important it is for future studies on the relationship between breastfeeding and celiac disease to incorporate data on breast milk composition. This type of data necessitates a longitudinal rather than retrospective study design, simply because people do not know the composition of the milk they were fed as an infant. The protective components in breast milk not only influence infant immune function at the time they are ingested, they also are integral to the development of the infant's immune system.

What's a Mother to Do?

Regardless of whether the lower than normal levels of sIgA and TGF- β 1 in breast milk from mothers with celiac disease are sufficient to promote oral tolerance of gluten, these levels are still higher than those in infant formula. Moreover, the mean concentration of sIgA in milk from mothers with celiac disease, as reported by Olivares et al (1), actually is well within the ranges reported from other populations at the same stage of lactation (4, 12, 13), and mean concentrations of TGF- β 1 are higher than values reported by Tomićić et al (4). Although their concentrations are lower than those from the healthy controls, milk protective factors from celiac disease mothers may still offer numerous benefits to their offspring. As we wait for more research, mothers with celiac disease should continue to breastfeed their infants, and preferably to continue breastfeeding during the time of gluten introduction to the infant's diet. Low levels of protective factors are better than none at all.

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Prescriptions for Bovine Lactoferrin

- The protein, lactoferrin, is an anti-microbial that appears to fight Crohn's disease, guard against necrotizing enterocolitis and reduce the severity of diarrhea.
- Lactoferrin promotes the growth and strengthening of bone, and prevents the breakdown of cartilage that occurs in osteoarthritis.
- Lactoferrin also fights cancer via at least two mechanisms.



In the United States, lactoferrin, a protein that is abundant in cow's milk, is added to a few sports drinks and as an anti-microbial agent on uncooked beef. But scientists are beginning to wonder whether it has therapeutic applications. Consider the range of complaints and diseases that it can to some extent alleviate: there is evidence that it acts against Crohn's disease, osteoarthritis and a suite of cancers. And the mechanisms behind its action are becoming ever clearer.

The Gut

First up, lactoferrin modulates the immune system by promoting the proliferation and activation of immune cells. In the mucous membrane of the intestines, lactoferrin increases the amount that cells make of various kinds of molecules known as cytokines, which also have the effect of activating cells of the immune system.

The evidence that lactoferrin holds promise for the treatment of Crohn's disease comes from researchers in Italy (1) who tested it on gut cells that had been invaded by a particular strain of bacteria—as is commonly the case in patients with Crohn's disease. Not only did lactoferrin modulate the inflammatory response of the intestinal cells, it directly scuppered bacterial invasion of them. The protein effectively stopped these bacteria from using a type of sticking mechanism, called “type 1 pili-mediated adherence,” by which they attach themselves to gut cells that they seek to invade.

Another intestinal problem for which lactoferrin could prove a saving grace is a devastating disease that is relatively common among premature babies. [Necrotizing enterocolitis](#) (NEC) occurs when patches of the intestinal tissue become inflamed, and in severe cases, die. In a study by Raghuvver and colleagues (2), the addition of lactoferrin to formula or to breast milk reduced the level of oxidizing products called free radicals, which are thought to contribute to the development of NEC. For various other reasons [adding lactoferrin to infant formula](#) appears to be a good idea (3).

Researchers in Columbia, Missouri, and in Orlando, Florida, reviewed (4) the wider evidence around NEC and lactoferrin in April. In particular, they note a multicentered clinical trial in which infants who would normally be considered at high risk of developing NEC were given bovine lactoferrin. These infants were less likely to get the disease than they otherwise would have been. More trials in which very low-birth weight infants are to be given lactoferrin are getting underway in Peru, Australia and New Zealand, as well as in the United States.

Lactoferrin may even be beneficial for reducing diarrhea in children without pre-existing health conditions. In a study published in the *Journal of Pediatrics*, 555 healthy toddlers in Peru were enrolled in a double-blind controlled trial in which they were randomized to receive twice-daily doses of bovine lactoferrin or placebo. Lactoferrin did not reduce the number of incidents of loose stool, but it did reduce the duration and the severity (5).

Bone and Nearby Tissues

In bone, lactoferrin promotes growth by causing bone tissue-making cells called osteoblasts to divide. Meanwhile, it inhibits the development of cells—called osteoclasts—that reabsorb bone. Additionally, lactoferrin appears to make bones stronger by lowering the production of a molecule called tumor necrosis factor, which in itself acts to give osteoclasts a boost.

This is only part of the logic behind why lactoferrin might be good for people suffering from osteoarthritis. This disease is also characterized by the degradation of articular cartilage. Recently, Yan et al (6) considered in the lab the effect of “bovine lactoferrin” (a partially broken down version of lactoferrin derived from cows milk) on human articular cartilage. Essentially, the team found that bovine lactoferrin reduced the cells' production of enzymes that degrade cartilage, via its effect on various other molecules and thus on target genes. They consequently conclude that, “bovine lactoferrin seems to hold promise as a disease-modifying molecule in prevention and/or treatment of degenerative joint diseases.”

Cancer

The mechanisms through which lactoferrin lowers the odds of certain cancers are probably far more diverse than for other diseases, in part because cancer tends to be a different disease in biomolecular terms in (and within) different sites around the body. The known mechanisms include lactoferrin prompting the suicide (apoptosis) of damaged cells and lactoferrin inhibiting the creation of new blood vessels that supply tumors. It achieves the latter by decreasing levels of a chemical called vascular endothelial growth factor (VEGF, for short).

For example, early work on how lactoferrin might aid in the treatment of lung cancer has focused on the VEGF mechanism. Tung et al (7) tested the protein first on cells in their lab, and then on transgenic mice that were genetically predisposed to develop human lung cancers. In both studies, lactoferrin not only blocked lung cell inflammation, but also inhibited the growth of blood vessels near the cancerous cells, which retarded delivery of food and oxygen to tumors.

Similar results were found in a study (8) of gastric cancer, except in this case it was the cell suicide mechanism at play. In this study, the researchers tested different fragments of protein that come loose when lactoferrin is digested. In their analysis, the most potent anti-gastric cancer peptide among this group was lactoferricin B25.

All these results add up to the suggestion that lactoferrin is worth pursuing in the search for new (and potentially quite cheap) drugs. Few other proteins have been linked to modulating the immune system, to fortifying bones and helping them to grow, and to fighting cancers in various organs. As a common protein in cow's milk, it has been safely consumed for thousands of years. With more research, a prescription for bovine lactoferrin may be just what the doctor orders.

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Adding Bovine Lactoferrin to the Mix

- The bovine version of an abundant protein in breast milk, called lactoferrin, has been authorized for inclusion in infant formula in several countries, but not yet in the US.
- Lactoferrin sequesters iron from bacteria and efficiently delivers it to nursing infants.
- Lactoferrin promotes intestinal development in early life.
- Laboratory tests show that bovine lactoferrin interacts with gut cells in essentially the same way as human lactoferrin.

Infant formula continues to improve toward the greater goal of reflecting the chemistry of real breast milk. Yet there is a clear distinction among brands marketed in the US compared with those in Spain, South Korea and Japan: the US brands lack an ingredient called lactoferrin, which has yet to be authorized by the FDA. Lactoferrin—the second most abundant protein in breast milk—is known to [confer all manner of benefits](#) (1), from cancer prevention to promoting healthy bones. Its main job, however, is binding iron.

Lactoferrin binds to iron because its structure has two distinct “lobes,” each able to pull in a highly positive Fe³⁺ (iron)ion. As a result, it can exist in three forms: with no bound iron, with one lobe bound to iron, or with an Fe³⁺ion in both lobes. This structure confers many of lactoferrin's disease-busting properties.



That lactoferrin binds Fe^{3+} ions so well means that most of the iron in breast milk is associated with it. As such, some researchers have raised the concern that infants who consume formula without lactoferrin might not absorb very much iron. Lactoferrin is especially abundant in early milk, known as colostrum, which contains about twice as much per liter as mature breast milk. The implication, therefore, is that the youngest infants need higher concentrations of the protein to nourish optimal development.

Why this is the case is partially answered by bacteria. Because lactoferrin attracts Fe^{3+} ions so effectively, it tends to outcompete other molecules, such as receptor molecules on the surfaces of bacteria. This can destabilize bacterial membranes, inhibit bacteria

from moving around or from entering human cells, or stop them from clumping together to form a film, which is necessary for some species to cause human illness.

Perhaps colostrum contains a higher concentration of lactoferrin than mature breast milk because the intestines of very young infants are fresh territory for bacteria to colonize—meaning that they require especially robust defense against pathogens. When lactoferrin is partially broken down by enzymes, as it is in infants, a modified version of it called “lactoferricin” is formed, and this has an even stronger antibacterial action than lactoferrin. In addition to lactoferricin, [the elaborate sugars associated with lactoferrin also have antibacterial potential against diverse microbes](#) (2).

Strangely, a select few species of non-pathogenic gut bacteria are actually favored by lactoferrin. Contrary to its effect on “bad” bacteria, in these cases lactoferrin actually promotes growth. And the growth of these non-pathogenic bacterial is in infants’ best interest since these bacteria can outcompete disease-causing species.

In addition to its antimicrobial features, lactoferrin is perhaps even more important to newborns because it promotes development of the intestinal tract. While still in the womb, babies receive nutrition from their mother’s placenta, and it is not until after birth that the intestines adapt. Lactoferrin coaxes the cells of the intestines to change and grow properly (3).

So where is the FDA with evaluating lactoferrin as an additive for infant formula? To date, the agency has received three “generally recognized as safe” (GRAS) notices for the use of human lactoferrin in food, although all were withdrawn before the FDA completed its evaluation. The more likely option is for the lactoferrin to come from cow’s milk—in other words, for infant formula in the US to eventually incorporate bovine lactoferrin. One such GRAS notice is currently under review.

A key issue in adding a molecule that evolved in a different mammal to infant formula is whether it has the same effects in humans as its human analog. This question was addressed by Bo Lönnerdal and his colleagues (4) at the University of California, Davis. They compared it to human lactoferrin, including how well it resists digestion in conditions similar to those in an infant’s digestive tract, and how well it binds to and is taken up by intestinal cells called Caco-2 cells. The results show that bovine lactoferrin behaved essentially the same as the human version.

In some ways, when the FDA waits behind analogous agencies around the world to approve a new food additive, it gains additional oversight in the form of the experiences of consumers of those countries where the substance is now legal. To be sure, randomized trials would be a good next step. But the FDA shouldn’t take too long over this. If lactoferrin’s function and abundance in breast milk is anything to go by, its potential health benefits if added to infant formula may be substantial.

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