



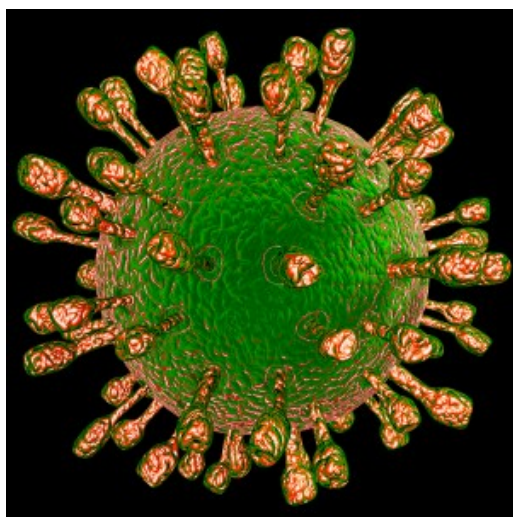
SPLASH! milk science update MARCH 2014 issue

This month's issue has stories of milk proteins that fight rotavirus, other milk proteins that relieve depression, the genetic troubles in selective breeding in cattle, and the benefits of milk fat digestion. Enjoy!

Sweet Revenge on Rotavirus

- Rotavirus infection is a major cause of severe diarrhea in young children and animals.
- Human rotavirus vaccines are emerging as an effective public health intervention to prevent infections.
- Milk contains sugars, proteins, and antibodies capable of inhibiting rotaviruses.
- Dairy-derived molecules may provide an additional means to reduce the burden of rotavirus infections, particularly in developing countries.

The main culprit behind viral gastroenteritis in young children is a group of viruses called rotaviruses that cause severe diarrhea and dehydration. Having evolved to recognize certain surface molecules on cells that line the small intestine, the rotaviruses latch onto these molecules to launch their warfare and invade the gut. However, mammals have evolved some biological weapons of their own to counter the viral attacks. For example, milk contains many remarkable ingredients, including sugars and proteins, which mimic the cell surface receptors that rotaviruses bind to in the gut. These milk goodies could help protect the infants from gastroenteritis by acting as decoys, mopping up the harmful rotaviruses.



Rotavirus

Each year, diarrhea caused by rotavirus infections afflicts millions of children worldwide and kills about half a million children under the age of five, mainly in developing countries (Tate et al., 2012). Rotaviruses are also responsible for serious illness in the young of other mammalian species, giving rise to significant economic losses in livestock production. Two human rotavirus vaccines became available in 2006 and have since proved highly effective (85–100%) in reducing the burden of rotavirus infections in industrialized western countries (Giaquinto et al., 2011). In developing countries, however, vaccination has been less effective (typically 40–70%), besides being hampered by high cost and other barriers to widespread distribution. Scientists and public health authorities are therefore continuing to search for additional means that can help combat rotavirus infections in humans as well as in animals.

Several scientific studies over the past few decades indicated that breastfeeding protects infants from the intestinal havoc brought on by rotaviruses. Researchers long attributed this anti-rotavirus effect to certain sugars, proteins, and antibodies present in milk, but unraveling the details of the molecular warfare is still ongoing.

Complex sugars engaged in combat

Some rotaviruses that infect animals recognize a type of simple sugar—a monosaccharide—called sialic acid. Sialic acids typically sit at the end of complex sugars, or oligosaccharides, chains of 3–10 monosaccharides, which are attached to the surface of many cells. Clutching onto such sialic acid-containing oligosaccharides, the viruses can break into the cells.

Researchers at the University of Illinois recently confirmed the hypothesis that sialic acid-containing oligosaccharides present in human milk could thwart such attacks on gut cells by the sialic acid-dependent rotaviruses (Hester et al., 2013). Based on tests in laboratory-grown cell cultures, they reported that blocking rotavirus attachment to cells was most likely the main counterstrategy of the milk sugars. Their data also indicated that even if the viruses prevailed in the binding step, the milk sugars might still put up a fight, for instance by interfering with the viral break-in into the cells or with the ability of rotaviruses to replicate within the cells.

Hester and colleagues concluded that milk sugars could be useful for preventing rotavirus infection in human infants as well as in young animals. They suggested that human milk sugars might even be used therapeutically, for instance in formulas, to reduce the severity and duration of the disease in children already infected with rotavirus. As part of their study, they developed an effective method to examine the rotavirus–milk sugar battle inside the gut of piglets. Following strict animal ethics guidelines, this new animal model provides a sensitive system for screening milk sugars and other ingredients for anti-rotavirus activity.

While this proof-of-concept study demonstrates positive effects of complex milk sugars against a sialic acid-dependent rotavirus that infects pigs, it shows no effect of milk sugars against a human rotavirus that does *not* need sialic acid to bind host cells. Because human rotaviruses are typically not dependent on sialic acid, there must be additional components in human milk that confer the observed protection of breastfed infants from gastroenteritis.

Focusing on three human rotaviruses that commonly cause gastroenteritis, researchers in Cincinnati, Ohio, hypothesized these viruses would home in on another sugar structure (Huang et al., 2012). They provided the first evidence that a protein protruding from the major human rotaviruses, spike protein VP8*, binds in a specific manner to a group of complex sugars known as histo-blood group antigens (HBGAs). HBGAs are present on the surfaces of red blood cells and cells that line the digestive, respiratory and genitourinary tracts.

The study by Huang et al. suggested that sialic acid-independent human rotaviruses might exploit HBGAs as binding partners to gain entry into cells. Incidentally, HBGAs are also present as free-floating oligosaccharides in several biological fluids, including milk. These investigators found that the HbGA-containing fractions of human milk samples bind to human rotavirus. So there is mounting evidence that milk contains an arsenal of complex sugars fit to fight against different types of rotaviruses.

Proteins packing a punch

Many of the proteins in milk are also thought to be key players in defense against pathogenic invaders. For example, the human protein lactadherin inhibits human rotaviruses (Kvistgaard et al., 2004). Lactadherin is one of the building blocks in the thin film of proteins and lipids surrounding the fat droplets in milk, known as the milk fat globule membrane.

Like many of the proteins in the milk fat globule membrane, lactadherin is a glycoprotein, meaning it is embellished with oligosaccharides. The sugars jutting out from the protein surface likely deserve at least part of the credit for the antiviral effect.

Several labs demonstrated that other glycoproteins, such as MUC1, that make up the milk fat globule membrane in both human and cow's milk also inhibit rotaviruses. These human and bovine glycoprotein cousins vary quite a bit in their ability to inhibit rotaviruses, probably because of differences in the protein structure as well as in the attached sugars (Kvistgaard et al., 2004). There is still a lot to be discovered about their anti-virus mechanism.

Antibodies—a commercial alternative?

Much effort has gone into attempts to develop commercial milk products with anti-infectious properties. In particular, cow's colostrum—the rich pre-milk fluid secreted during the first few days of lactation that contains high amounts of antibodies—has garnered great interest. Antibodies, also known as immunoglobulins, are glycoproteins on a search-and-destroy mission, capturing foreign invaders such as viruses or bacteria by locking onto specific target molecules on their surface.

A potential barrier to widespread use of colostrum-derived products is their high cost given the precious nature of the raw material. Interestingly, though, a team of researchers from Denmark and Spain demonstrated that rotavirus-neutralizing antibodies were present in an ordinary, commercial whey product, suggesting there might be low-cost alternatives to colostrum-derived antibodies (Bojsen et al., 2007).

However, rotavirus antibodies are easily destroyed by heat treatment (pasteurization), which is used for hygienic reasons in the preparation of commercial bovine whey products. Bojsen and colleagues hence emphasized that it is crucial for manufacturers to optimize the heating conditions to maintain a relevant anti-rotavirus effect.

Clearly, apart from providing nutrition to nursing infants, both human and cow's milk are packed with defense molecules, some of which have evolved specialized revenge mechanisms in the arms race with rotaviruses. Evidently, rotaviruses are formidable enemies that have too often had the upper hand. But with the emerging promise of human rotavirus vaccines and the potential to boost their success in appropriate combination with breastfeeding practices and advanced milk-derived products, rotaviruses now seem to have the cards stacked against them.

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Drink Milk, Be Merry?

- Dairy products contain various substances that can alleviate depressive symptoms.
- There is increasing evidence that some such substances, called beta-casomorphins, can make their way from the gut to the brain and act on serotonin receptors.
- Small-scale studies in humans have found beneficial effects of another milk protein, alpha-lactalbumin, on cognitive function in formerly depressed and in stress-vulnerable people.

When people take drugs to treat depression or stress, they are trying to change the levels of certain chemicals in the brain through which nerve cells communicate. Serotonin is probably the most important as well as the most famous of these chemicals. Recently, evidence has emerged that people have different versions of the gene for the protein that moves serotonin into brain cells, and correspondingly different propensities for depression. More optimistically, evidence has also emerged that eating certain dairy products—as well as exercising and spending time in sunlight—can raise serotonin levels and thus potentially reduce or act preventatively against depression.

Various milk components appear to ward off the blues. Vitamin D, for example, lessens seasonal affective disorder. This vitamin is made in the body when skin is exposed to sunlight or, more specifically, when ultraviolet B radiation breaks down the substance, 7-dehydrocholesterol. In summer, there is sufficient sunshine to make this happen in such quantities that the hormone resulting from 7-dehydrocholesterol break down affects the brain's dorsal raphe nucleus, and consequently keeps a forebrain network called the ascending serotonergic system in the mode of making you feel happy. In winter, the lower sunlight levels mean that this pathway is less active, leading some people to feel depressed. But eating vitamin D, mainly as fish oils and fatty fish, or drinking vitamin D-supplemented milk and orange juice, can help¹.

Milk also contains fragments of protein that activate the same biochemical receptors in the nervous system as do morphine and opiate drugs. These fragments are present in relatively high levels in all sorts of well-known types of cheese. The best studied are the beta-casomorphins, which have surprisingly strong effects. Just five years ago, the conventional wisdom went that these fragments are entirely ravished by enzymes in the adult—but not the infant—gut and thus fail to make the journey across the intestinal wall into the body.



However, a 2009 study of cheese by Sienkiewicz-Szlapka et al. revealed that this line of reasoning is probably nonsense². If beta-casomorphins do find their way into the cheese-eater's circulation, as this team's work suggests, then it is quite likely that they also make it into parts of the brain³. Another key piece of research was contributed in 2013 by a group of Irish researchers. They demonstrated that components of milk really do activate serotonin receptors in cells, although those cells were in test tubes in a laboratory (as opposed to being inside a brain)⁴. Together, these various studies set up a plausible mechanism by which a long evening with a cheese fondue might, in a very mild way, act rather like hooking yourself up to a dilute morphine drip.

Does this add up to medically relevant benefits? Potentially, although the different avenues of research so far do not connect to each other seamlessly. Dutch scientists are, for example, probing whether another protein in milk called alpha-lactalbumin might help people recover cognitive performance. There are two recent studies of note here: one in which alpha-lactalbumin supplements were used to try to raise the decreased cognitive function of people who had come out of a period of depression; the second study attempted to improve the cognitive performance of particularly stress-prone students. The link between alpha-lactalbumin and serotonin levels is simple. Alpha-lactalbumin is rich in tryptophan, another protein that is a precursor of serotonin. Thus, raising alpha-lactalbumin levels raises tryptophan levels, and therefore those of serotonin.

In the second study, Rob Markus of the University of Maastricht and colleagues⁶ formally measured the "neuroticism" of university students, defined as how disposed the students were to seeing events as alarming and to experiencing aversive emotional states. They then tested the memories of students among the most and the least neurotic. This testing happened before and after the students either consumed normal chocolate milk as part of their diet, or chocolate milk doped with alpha-lactalbumin. Only the students who were in the most neurotic group and who also consumed alpha-lactalbumin-rich milk saw significant improvement on the memory test.

The team's explanation for this finding was that the most stress-vulnerable students probably had depleted brain serotonin, and, under chronic stress, their brains were more sensitive to the molecule. Therefore, when they ate large amounts of tryptophan, this group experienced the largest changes.

The number of human subjects tested in these Dutch experiments was small—too small to justify any broad recommendations based on the results. But the results in each study are worth following up. Over time, the lab work into serotonin's effects and the foodstuffs that can affect serotonin levels is likely to correspond ever more closely to those measured in human trials as opposed to cells in test tubes. The future of this field, in short, looks rather happy.

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The Ups and Downs of Genetic Selection in Dairy Cattle

- Lower levels of fertility have been increasing in dairy herds.
- Selective breeding has apparently contributed to this fall of fertility in some breeds.
- A missing region of DNA that is linked to fertility rates was identified in Nordic Red cattle.
- The unexpected higher prevalence of this mutation may be explained by its effect on increasing milk production.

Selective breeding of animals has underpinned enormous production gains and farming efficiencies in dairy. But what has been the impact of intensive selection on the modern dairy cow? Armed with recent advances in genomics, scientists are beginning to answer this question.

One of the most significant issues in dairy production in recent times is a falling rate of cow fertility. Of course, this is a challenge for farmers, who must manage the pregnancy and lactation phases of their herds to maintain levels of milk production and hence the farm's economic viability. Physiologists and nutritionists studying this area have identified that an underlying cause is the competition for energy supply between what is required to establish a pregnancy and the demands of the udder during peak milk production. So, the more energy that goes into producing milk, the less energy is available to devote to ovulation, implantation and embryo development. However, in Nordic Red dairy cattle, Kadri et al. from Aarhus University in Denmark, along with colleagues from Belgium and Finland, have now discovered another explanation. In the January 2014 issue of *PLoS Genetics* (1), they described a section of the bovine genome that simultaneously contributes to higher levels of milk production and lower levels of fertility. So, developing herds based on milk produced has meant that, as milk output has gone up, fertility has gone down in these breeds.



A liquid nitrogen bank containing straws of frozen bull semen.

The combination of genetics and artificial insemination has brought substantial and widespread improvements in dairy production. A champion bull may contribute to hundreds, or even thousands, of daughters in dairy herds, nationally or sometimes internationally. This improvement in dairy production has been through several phases of development, and much of the gain in the past 25–30 years has been on the basis of bull-proving systems that estimate the genetic “value” of a bull based on the productivity of progeny. Recently, this approach has been complemented, or in some cases replaced, by the introduction of methods based on genomic selection (2–4). Genomic selection uses DNA-based methods rather than progeny testing (5), and has been made possible by the bovine sequencing project and the associated development of powerful, low-cost genotyping tools (6, 7). Whatever the system, these procedures have been developed to improve returns for farmers by making farming systems more efficient, so it is not surprising that selection has been heavily weighted toward production traits that deliver more milk, or milk with a particular quality, e.g. increased milk fat, or higher milk protein yield. What has been known by geneticists for many years is that certain traits overlap, i.e. there are regions in the genome that contribute to more than one outcome, and sometimes the same region can have an opposing or antagonistic effect on these traits. What was described by Kadri et al. is a prime example of how antagonistic effects may happen in dairy cattle.

Kadri et al. began with a traditional approach to investigate the genetic basis of fertility in dairy cattle. This approach has been notoriously difficult because measures of fertility in dairy cows vary considerably, and the way in which it is measured does not correspond closely with genetic effects (low heritability). However, these investigators had collated an excellent set of data from a very large number of records and several dairy breeds. When the data were analyzed, a region of the genome stood out that was statistically associated with rates of conception. Then the detailed detective work started. By combing through records that might in many circumstances have been filtered out before analysis, they discovered that in the Nordic Red cattle, there was a relatively small piece of DNA missing in some animals. This is not unusual; if genome sequences are compared between groups of individuals, there are many regions that may be duplicated or deleted in some animals and not others. However, in this case, when they compared the fertility data, they found that the missing piece accounted for low levels of fertility. To their surprise, they also found that, despite it contributing to low fertility rates, the missing piece of DNA was present in a lot of animals. Why would an apparently deleterious mutation not get weeded out of herds? The most likely explanation was that it was under positive selection, that is, it was providing benefits to production. Indeed, when Kadri et al. reanalyzed the data looking at milk production traits, this very same region was contributing to higher levels of milk production.

Of course higher milk production could only happen in animals that had inherited one copy of the deletion. When deleted regions contain genes essential for embryo survival, a calf will not be born if DNA containing the deleted region is inherited from both sire and dam. So, in the animals that were studied, those that had inherited a chromosome with a deletion in that region, and one without the deletion, they not only survived, but grew up to be cows that produced impressive volumes of milk. When selection based on milk yield progressed over many generations, the deletion was positively selected and its occurrence in the dairy herds gradually increased. As more animals with the deletion appeared in the herd, the overall production of milk may have increased, but overall fertility decreased. What can cause both positive and negative effects? This usually indicates a gene with a regulatory function. There are four genes in this region of the genome that come under consideration as a first step to understanding the biology. Kadri et al. suggest that a gene called RNASEH2B may provide the explanation, because it also prevents embryo development when deleted in mice. However, they do not rule out other potential explanations, including effects from neighboring genes, and there certainly appears to be others around that region that may have regulatory functions. For now, it remains a mystery, but like any good detective story, all will be revealed in the final chapter.

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Milk Fat Built for Digestion

- **Digestion of fat requires that large fat molecules be broken down into smaller molecules.**
- **Milk fats are different from other dietary fats because they are emulsified prior to digestion.**
- **A new study demonstrates that milk fats self-assemble into highly ordered nanostructures, even in the absence of bile.**
- **Milk can provide essential fat and fat-soluble vitamins to people with low bile production (infants, elderly, and people with gallbladder or liver disease).**

If left to settle, fresh whole milk separates out into an aqueous phase on the bottom and a lipid (or cream) phase on the top. The lipid phase adds more than calories to milk. Hidden in this lipid layer are brain-building molecules like DHA and fat-soluble vitamins like vitamin A. But in order for these lipid-bound components to do their job, they need to get from the digestive tract to the circulatory system. Just how is this accomplished?

For all the research that has been done on the importance of milk fat for infant growth and development, we know surprisingly little about the process of milk fat digestion. A new study by Salentinig et al. (2013), using store-bought homogenized and pasteurized cow's milk, demonstrates for the first time that fats in milk self-assemble to form highly ordered "nanostructures" not seen in the digestion of other dietary fats. And importantly for consumers of milk, these nanostructures increase the absorption of milk fats and all the other good things that are part of the lipid layer. Milk fat, it appears, is built for digestion.

Fat digestion: size matters

Fat digestion requires making fats more soluble so they can be absorbed into the intestine and transferred to the circulatory system. One of the primary ways this is accomplished is through the activity of digestive enzymes called lipases. Lipases break down the most common type of dietary fat, triglycerides (three fatty acids on a glycerol backbone), into a monoglyceride (one fatty acid and a glycerol) and two free fatty acids, which can then be absorbed by the cells of the small intestine.

There's just one catch—lipase enzymes are water-soluble and, therefore, only able to work on the surface of the fat molecule. But in the aqueous environment of the digestive tract, the hydrophobic (“water-fearing”) fat molecules are attracted to one another and form large fat masses. Here's where bile enters the story (or, rather, the intestine). Bile breaks large fat globules into smaller fat particles in a process known as emulsification. These emulsified fat droplets have a larger surface area (relative to their internal volume) and thus can more easily be digested by lipase.

From micro to nano

When it comes to fat digestion, the smaller the better. Emulsified fats—those that have been broken down into smaller droplets—are more rapidly digested by lipase. But milk fat, unlike fat from vegetables or animals, is already present as part of an emulsion (small fat droplets dispersed into an aqueous solution). How might milk fat's unique structure influence its digestion?

To address this question, Salentinig et al. (2013) did experiments in test tubes to simulate milk digestion by the intestine. When milk fat enters the digestive tract, they are micrometer-sized emulsion particles. However, when they reached the intestine, Salentinig et al. made a surprising discovery. Instead of grouping together to form larger fat masses, milk fat self-assembled into even smaller emulsion droplets. These nanometer-sized structures (or nanostructures) have a high internal surface area, facilitating the action of lipase.

The key phrase to highlight from the previous paragraph is “self-assembled.” Although smaller fat molecules are usually formed by the action of bile, Salentinig et al. observed the formation of these nanostructures even in simulations of milk fat digestion that lacked the addition of bile acids.



Digestive system

No bile, no problem

Why might other dietary fats require bile for digestion whereas milk fat does not? Salentinig et al. propose an adaptive explanation. Newborns and infants have reduced bile production, but are also dependent upon milk fats for brain growth and development, immunity and even skeletal growth. The self-assembly of nanometer-sized milk fats may have evolved as a compensatory mechanism to ensure the delivery of fatty acids, fat-soluble vitamins and other bioactive components from milk to the developing infant's circulatory system (Salentinig et al., 2013).

This is an exciting evolutionary hypothesis, suggesting that milk fat digestion may be adapted to the digestive chemistry of the infant gut. But Salentinig et al. are quick to highlight that infants are not the only consumers of milk that may have compromised bile production. Humans living with gall bladder or liver issues and the elderly have difficulty with fat digestion because of poor bile production. If bile salts are not required for milk fat digestion in adults, milk and milk-derived products such as yogurt and cheese may provide superior sources of dietary fat. Nanostructure formation might have evolved as a mechanism to facilitate milk fat digestion in infants, but it may prove to be advantageous for millions of adults.

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