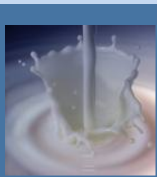
SPLASH! milk science update: July 2015 Issue



SPLASH! milk science update
July 2015 Issue

This month's issue features how human milk sugars protect against food allergies in mice, how milk may be the ultimate post-workout nutrition, making sense of dairy biosystems, and breast milk products of the future.

Human Milk Sugars Can Protect Against Food Allergies in Mice

- **Sugars present in human milk have been previously shown to influence the immune system both directly and indirectly.**
- **A new study finds that two sugars present in human milk can reduce the severity of food allergy symptoms in mice.**
- **The sugars, 2'-fucosyllactose and 6'-siallylactose, modulated the mouse immune system to decrease inflammation and increase tolerance to allergens.**
- **Food allergies affect a substantial proportion of the population, and there are few therapies available.**
- **If the study's results can be replicated in humans, this could potentially lead to specific milk sugars being used as part of therapies to protect against food allergies.**

Food allergies affect a substantial proportion of the population, and there are few treatments available (1,2). A new study finds that two sugars present in human milk can help protect against food allergies and reduce the severity of food allergy symptoms in mice (3). If the results can be replicated in humans, these milk sugars could potentially lead to new anti-allergy therapies.

Drinking human milk has previously been shown to influence the immune system. "There was some evidence to suggest that human milk can protect infants from allergic disease," says Paul Forsythe, an immunologist at McMaster University who led the study. Forsythe and his colleagues set out to figure out which component of milk might have a protective effect on allergies, and decided to focus on milk sugars.

Certain types of sugars, called oligosaccharides, form the third largest component of human milk (4). These sugars serve as food for beneficial bacteria in the infant gut, thereby increasing the abundance of these bacteria and indirectly influencing the infant immune system (5,6). Recent work has shown that these sugars can also act directly on immune cells (7,8,9,10). Forsythe wondered if either of these effects could allow these sugars to protect infants from allergic disease.

Forsythe and his colleagues decided to test the effects of two oligosaccharides, 2'-fucosyllactose and 6'-siallylactose, which are particularly abundant in human milk. They focused on a food allergy model because ingested milk ends up in the intestine, where milk sugars could directly affect the immune response to food allergens. "We think that's the most obvious one to go for," Forsythe says.

The researchers conducted their tests on mice whose immune systems had been trained to react to egg white protein. They found that the mice treated orally with the two sugars had significantly reduced symptoms of intestinal allergy, such as diarrhea and hypothermia. Forsythe and his colleagues then tried to decipher the mechanisms by which these sugars might be affecting food allergy symptoms. They hypothesized that the sugars could either act directly on immune cells, or indirectly by affecting the gut microbiota composition, which has previously been shown to be able to affect allergy symptoms (11,12,13,14).

The researchers found that the sugars appeared to have a direct effect on the immune system, suppressing the inflammatory response and creating an immune environment that was protective against allergies. "They induce an increase in regulatory T cells whose job is to suppress inflammation," Forsythe says. The sugars also induced an increase in a different type of immune cell involved in tolerance against allergies.

Treatment with the sugars also suppressed the activation of mast cells, important immune cells involved in food allergies (15,16). “These are the cells that are responsible for most of the symptoms of allergies,” Forsythe says. “They release inflammatory mediators when they respond to whatever you are allergic to, and the mediators cause the allergic symptoms,” he says. “Feeding these oligosaccharides somehow stabilizes these mast cells so they don't release their inflammatory mediators,” Forsythe says.

Forsythe and his colleagues are starting to look at whether these milk sugars might also be affecting allergies indirectly by influencing the gut microbiome. In addition, the researchers plan to examine whether these effects could extend beyond food allergies to other allergic diseases such as asthma, perhaps through more systemic effects.

Forsythe says he plans to see if some of the sugars’ effects can be replicated in humans, and eventually hopes to test the effects of these milk sugars in human clinical trials. If the results hold true in humans, they could potentially lead to a way to use these sugars as dietary supplements that might help protect against allergies, Forsythe says. “It could maybe increase the exposure level so that you can be exposed to more of the antigen—the thing that you're allergic to—before you have an allergic response,” he says. “So it may have some kind of therapeutic effect,” Forsythe says.

Any protective or therapeutic benefits gained from these milk sugars could prove very helpful. “There are really limited therapies available for food allergies at the moment, so anything that can help is good,” Forsythe says.

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Milk Nutrients Augment Muscle Growth and Recovery

- **Whey proteins found in milk contain a high proportion of amino acids known to play a role in muscle tissue protein synthesis.**
- **Study subjects supplemented with whey protein during resistance training programs show greater increases in lean body mass than those supplemented with either soy protein or carbohydrates.**
- **Whey proteins combined with carbohydrates have been demonstrated to improve recovery after workouts, including decreases in muscle functional capacity.**
- **Milk may be an ideal recovery beverage for resistance and endurance training because milk is a whole food source of whey, slowly digested casein proteins, and carbohydrates that provide fuel for growing muscles.**

As anyone who has watched a professional bodybuilding contest can attest, muscle tissue is quite adaptable. In fact, muscle has been called the most adaptable tissue in the human body because it is constantly responding to mechanical strain. When a muscle is placed under strain (like a bicep curl or bench press), the muscle fibers are damaged and respond by fusing together and increasing in mass. Because muscle fibers are made of protein, this repair and growth process can be augmented by nutrition. Decades of research have investigated just which nutrients may best support muscle development, with the bulk of the research focused on milk-derived whey proteins. From everyday gym rats to professional athletes, whey protein is associated with gains in muscle mass and decreases in muscle soreness. And milk may yield even more benefits than whey protein supplements alone, offering up whey plus slow-digesting casein proteins, carbohydrates, and electrolytes. Don't tell the health food stores, but the best fuel for muscles could be in the grocery store's dairy aisle.

No pain, no gain

As strange as it sounds, a good number of us purposely inflict damage to our muscle tissue on a daily basis in an activity called strength training. A set of bicep curls or leg presses places the associated muscle fibers under strain, which damages the fibers. To repair themselves, the muscle fibers fuse together and increase in diameter and length, thereby creating a larger muscle (1). This gain does not come without pain. Damaged muscle fibers are a site of inflammation that normally lasts between one and three days. With this inflammation comes soreness, tenderness, decreased mobility of the muscle group, and subsequently decreases in agility and muscle performance. Researchers refer to this as delayed onset muscle soreness (DOMS) and it is considered a normal side effect of the muscle rebuilding process (1-3).

The science of recovery nutrition is based on the cellular processes associated with muscle development. While we may normally picture a cell as a sphere, muscle cells (commonly referred to in the literature simply as muscle fibers) are actually shaped like tubes. Each tubular muscle fiber is itself composed of hundreds of tube-like structures called myofibrils, and within these myofibrils are thin strands of proteins. [Picture an empty paper towel roll (the muscle fiber), filled with drinking straws (the myofibrils), which are in turn filled with uncooked spaghetti noodles (the proteins)]. Muscle growth is an increase in the diameter of the muscle fiber, which is accomplished by an increase in myofibril size due to increased protein synthesis (the addition of more spaghetti noodles means wider straws, which means a wider paper towel roll). Muscle growth is thus highly dependent on protein synthesis within muscle tissue (1).

Getting more bang out of your workout buck

It is not surprising, then, that a great deal of research has gone into investigating particular nutrients that can activate, enhance, and support muscle protein synthesis in conjunction with resistance exercise (4). In a meta-analysis of 22 studies including nearly 700 different subjects, Cermak et al. (4) found that protein ingestion after even a single instance of resistance exercise functioned to inhibit muscle breakdown and increase muscle protein synthesis (or, an overall anabolic effect). Although there were some discrepancies across the studies in outcome measurements, results from studies that involved training programs longer than six weeks overwhelmingly support the hypothesis that protein supplementation during resistance training increases muscle mass (by increasing fiber diameter) and muscle strength.

But will just any protein do? In Cermak et al.'s meta-analysis (4), the majority of the studies reviewed (18 out of the 22) included a whey protein supplement. Whey proteins are only found in milk and are included in nutritional intervention experiments because of their unique amino acid composition. Whey proteins are especially rich in branched chain amino acids (BCAA), including leucine. Protein synthesis begins in the nucleus when the DNA receives a chemical signal that it needs to manufacture proteins. Leucine and other BCAA found in whey are believed to act as this molecular signal to the many nuclei of muscle fibers (5, 6).

In one of the longest nutritional intervention experiments to date, Volk et al. (6) demonstrate the role of leucine and whey protein in activating muscle protein synthesis (an anabolic action) as well as preventing muscle protein breakdown (an anti-catabolic action). One hundred and forty-seven men and women between the ages of 18 and 35 were placed into one of three supplement categories: whey, soy, or carbohydrate. Regardless of the supplement type, each study subject completed 96 resistance-training workouts over approximately nine months with a professional trainer. The researchers went to great lengths to ensure as much homogeneity across the groups as possible, particularly in total protein consumption before supplementation. Protein intake was approximately 1.4 grams (g) per kilogram (kg) of body weight in the soy and whey groups compared to 1.2 g/kg in the carbohydrate group.

At the end of the study period, all three groups had increased their lean body mass, but the largest increase was found in the whey group. Interestingly, there was no significant difference in the amount of lean body mass gained between the soy protein and carbohydrate groups, despite the soy group consuming approximately 22 g more protein per day. Volk et al. (3) use this finding to argue that it is not the total grams of protein that matter for muscle growth, but the types of amino acids in those proteins. The greater gain in lean mass in the whey supplement group was attributed specifically to higher concentrations of BCAA in whey compared to soy protein (approximately 50% more) (6). Subjects in the whey group had more than two-fold higher post-workout plasma leucine concentrations than the soy group. Moreover, fasting leucine levels were also highest in the whey group, indicative of a higher overall leucine availability. Volk et al. (6) suggest that the anabolic surges that occur after a workout, and the overall greater exposure of muscles to leucine among the whey supplement subjects, led to increased net muscle protein balance (more protein synthesis, less protein breakdown).

Milk: whey, and way more

Cow's milk is a whole food source of whey protein, so it stands to reason it may have similar benefits to muscle development as whey supplements. But are there any additional benefits for consuming it straight from the source as opposed to the powdered form? Several studies have investigated milk's role in muscle development, focusing specifically on the recovery process. Recall that muscle growth is initiated by muscle damage. As muscles repair themselves and grow, there is a period of decreased muscle function, which can manifest itself as reduced agility and reduced strength in the damaged muscle groups. For the everyday gym goer, this may be a small inconvenience. But for trainers and coaches of professional athletes, decreasing the recovery period and limiting the effects of exercise induced muscle damage (EIMD) is of critical importance.

Milk contains both proteins and carbohydrates, the combination of which is believed to play a role in increasing the repair of muscle protein structures and decreasing protein degradation within muscle tissue (2, 7, 8). Further, consuming proteins alongside carbohydrates can improve subsequent endurance or strength exercise performance. While whey alone may improve gains in lean body mass, milk's combination of rapidly digested whey proteins, slowly digested casein proteins, and carbohydrates (lactose) work together to improve muscle recovery and future performance.

Cockburn et al. (2) found that the consumption of 500 ml of low-fat milk (approximately 2 glasses) immediately after muscle-damaging exercise limited reductions in muscle function measured 48 and 72 hours later compared to a placebo drink. The same research group also identified a positive effect of milk consumption on muscle recovery in athletes involved in field-based sports, such as soccer and rugby (7). Participants completed a 90-minute shuttle run activity one week before and 48 hours after engaging in a muscle damaging exercise that targeted the hamstrings. The shuttle run was designed to simulate the bursts of speed and physical endurance seen in field-based sports. As in the previous study, 500 ml of milk or a placebo was consumed immediately after completing the muscle damaging exercise. Comparing shuttle run performance before and after muscle damage was used as a proxy for how well each athlete would be able to perform in an actual match two days after training. In addition, they also measured agility and overall muscle force in the hamstrings. While the groups did not differ in several of the outcome measurements (e.g., countermovement jump height and muscle soreness), the study did find that milk consumption limited the reductions in muscle performance that are required for field-based sports, such as sprint times during the shuttle run.

The timing of milk consumption directly after EIMD is an important feature in these (2, 7) and many other studies (5, 8, 9) that look at milk as a recovery beverage. After resistance or endurance training, muscles have decreased energy (glycogen) stores and need immediate refueling in the form of carbohydrates. Delays in providing damaged muscles with carbohydrates are associated with increased recovery periods (9). Milk also has demonstrated benefits in post-exercise hydration, outperforming other well-known carbohydrate beverages including Gatorade.

Milk as recovery nutrition

Professional and recreational athletes alike are interested in finding the ultimate recovery beverage. While there are dedicated aisles in health food stores to muscle building powders and others to carbohydrate recovery drinks, milk may be the only beverage that can boast the ability to play a role in both. And believe it or not, chocolate milk may be an even better recovery drink, particularly for endurance sport athletes such as runners and cyclists, because it offers all the same essential amino acids but has more carbohydrates than regular milk (10). It might not come in fancy packaging or have a catchy name, but milk might be the next big thing in recovery nutrition.

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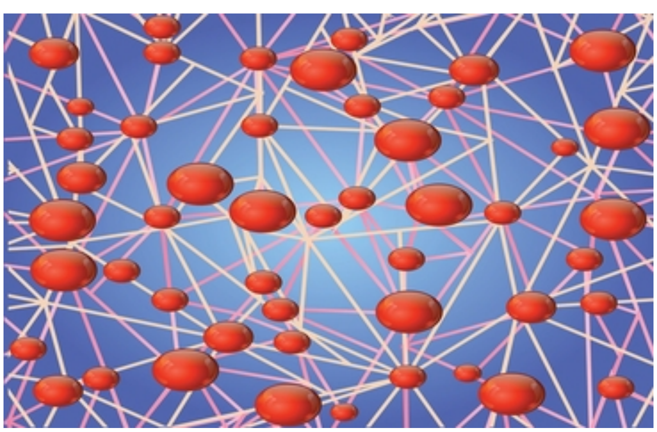
Making Sense of Dairy Biosystems

- **Genomic technologies produce lots of data.**
- **Putting all this data together is a complex problem that requires using both mathematics and statistics, as well as computer science and informatics.**
- **Collating biological data and extracting the relevant information is referred to as systems biology.**
- **Using systems biology to analyze animal traits may enhance dairy cow production.**

We live in an information-rich world. Each of us is capable of downloading gigabytes of data on our mobile or desktop devices each day. The upswing in data generation is also true of dairy science, which has moved into the big data realm. My students can create more data in an afternoon than I created in an entire PhD project when I was a student. Needless to say, capturing and analyzing this data is both challenging and rewarding. Since genomic data became more accessible, a number of approaches have been developed to bring the data together in useful ways (see e.g. [1,2]). Gradually these approaches have become more sophisticated and insightful. A recent study by Widmann et al. [3] provides a great example of how integrating different sources of large-scale genomic data can shed light on how dairy cows convert their feed into milk.



Animal feed represents a significant cost on the farm, so making sure that the feed is appropriate for the animal's needs, and that the cow uses the feed efficiently, is a major concern to farmers. Widmann et al. [3] measured the feed intake and the impact it had on animal production traits in an experimental cattle herd. They set out to determine how the utilization of that feed by the cow was related to its genetic background. To do this, they developed an approach that used a range of related measurements, such as how much the cows ate above what they require for basic physiological functions, or how much energy was ingested. Using these measurements, they developed an integrated measure of all the things that might affect efficient use of the consumed feed.

The genetic type (genotype) of each cow was also measured with a test that covered the entire genome of each animal. They generated approximately 130 million data points from this genotyping test; and nearly 50,000 data points for daily weight gain and feed intake, plus another 50,000 data points for measurements of metabolites (the by-products of chemical reactions that occur in cells). Each measurement was analyzed for every genotype data point, generating a total of 13,035,000,000,000 (1.3x10^13) results. How can such a huge number of analyses be managed and interpreted? The scientists used a series of mathematical and statistical methods to condense the data and extract meaningful information. Generically, this approach to analysis of biological processes is referred to as systems biology.

They first analyzed two genes that had previously been implicated in metabolism and growth. Variants of these genes, known as NCAPG and GDF8, showed a significant effect on feed conversion in the tested animals. The scientists then assembled the very large data set for a multi-stage analysis. To do this, they first looked at those points that indicated that they could influence feed efficiency related traits. From there, they developed a table from data that showed how functionally connected the genes close to those genetic markers were. This information was incorporated into the next stage of analysis, which gave the scientists a list of genes organized in a hierarchy or network indicating the relative importance of the surrounding genetic regions. These networks reflected what was happening within the physiological systems that the animals used to convert feed into body weight (or by extrapolation to milk). The complex set of data was simplified with this method, but interpretation of the results still captured the complexity of the system.

Using this approach they discovered a highly interconnected network of genes that had a significant impact on the efficient use of feed by the animals in the herd. When looking closely at the network, it was apparent that there were two key drivers or controllers of many key genes: TP53 and TGFβ. This is an interesting finding because we know that TP53 is a gene that regulates many processes inside cells, and because of this powerful role, it causes cancer if it becomes mutated. TGFβ is a more surprising finding; it is more enigmatic and has a range of functions that seem to depend on where and when it is activated. When considering both the genes, and the complete networks, the findings are intriguing and will no doubt stimulate follow-up studies.

Ultimately, developing selective breeding programs that incorporate information based on complex systems will provide dairy cattle breeders and farmers with cows that reach their full potential for the efficient production of milk. This will provide these farmers with improvements that contribute to highly profitable and sustainable dairy farms.

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The Breast Milk Products of the Future

- **Several companies are now selling products made with human breast milk.**
- **These range from simply sterilized and otherwise unaltered milk, to long-life versions and fortified milk for premature babies.**
- **The market is in its early days, but key questions remain about affordability and, most importantly, the biological activity of the milk products after processing.**

For several years now, as work on the health benefits of the constituents of breast milk has progressed, researchers have wondered whether their findings might benefit infants in ways other than encouraging moms and NICUs to feed them breast milk. In short, scientists have imagined that breast milk's oligosaccharides, unusual and complex proteins and so on, could be bottled in some way, and provided quasi-medicinally to infants with particular needs, and perhaps even to sick adults. Science aside, the field has always been held back by a shortage of available human milk. But, with the Internet acting as an aggregator of many small-scale suppliers (mothers) a new world of breast milk-based products is beginning to open up.

This new world will have to grapple with a number of questions: Who should be able to access the products? To whom will they be prohibitively expensive? How practically useful will they be in different settings? And in the process of making them practically useful—for example, in removing the need for refrigeration—will the active components that give breast milk its celebrated goodness lose some or all of their biological activity?

At present, there are a few companies working on human oligosaccharide products, which are still a little way off. There are companies doing nothing more complicated than trying to ramp up the more traditional non-profit milk bank model. Their aim is to increase supply by paying mothers for their effort, and getting properly sterilized or pasteurized milk to other mothers who seek it at reasonably low cost. In between, are the companies adapting milk in some way; they are producing shelf-stable liquid breast milk, or freeze-dried breast milk, both of which are intended to last many months. One has developed a specialized 'human milk cream', fortified specifically for very young infants.

In the 'nothing more complicated' category, the International Milk Bank aims to be a bulk supplier of standard breast milk, properly treated to rid of any germs and screened to guard against traces of illicit drugs or alcohol. In this sense it will compete more directly with non-profit banks, such as the 18 banks that compose HMBANA (Human Milk Banking Association of North America). Run out of Reno, Nevada, by Glenn Snow, the International Milk Bank intends to start selling sterilized breast milk to hospitals and to individuals in the United States by next year, and then to the rest of the world. Snow's aim is clear; he wants to "end the shortage", as he puts it, with safety as a top priority.

It is hard to judge this model until it really gets going. When it enters the market, it will meet Medolac, based in Lake Oswego, Oregon, which makes shelf-stable milk and has been distributing to hospitals since last October. Medolac also sells to parents at home. Shelf-stable milk doesn't need to be refrigerated until it is opened, and thereafter lasts for about a week. Medolac has tested the macronutrient retention of its product at seven months, and found it to be no different to the product that emerges straight after processing. But the idea is for it to be stored at room temperature for up to three years. "I wanted to create a product that was as easy to use in the hospital as infant formula," explains Elena Medo, Medolac's CEO.

Mammalia Breast Milk, another for-profit venture, has a similar philosophy of making breast milk last like infant formula does, and expanding distribution. It hopes to start shipping freeze-dried breast milk around late summer or early fall of this year. Rachel Ellen, the company's founder, explains that the main benefit of freeze-drying is that viruses and bacteria are unable to grow during storage. "Unlike milk banks that only dispense breast milk by prescription; we want to make breast milk accessible to anyone who wants it. We understand that breast milk has a unique combination of nutrients essential to a child's health, and cannot be duplicated by laboratory formula." Ellen is careful to point out that she has no wish for freeze-dried breast milk to replace the real thing where a mom is able to feed her infant.

The big question, however, is the extent to which different kinds of processing and storage actually preserve the biological activity of breast milk's most important components. A full answer to this question cannot yet be provided. Freeze drying does significantly lower ascorbic acid and vitamin C levels, and the milk's antioxidant capacity is slightly decreased, says Ellen, although fatty acid composition is unaffected. Medolac has sent its product to Lars Bode at the University of California, San Diego, to evaluate the oligosaccharide component. Medo says that Bode compared the product to milk donated to a milk bank in San José, and found high levels and a broad range of oligosaccharides in the Medolac milk, despite its processing. Proteins present a tougher challenge, though. Growth factors, for example, have been measured and found to retain some of their original activity in shelf-stable milk—between 18% and 48%, according to Medo. She complains that the rest of the industry is shy of providing samples for a "head-to-head" analysis. "Our goal is to have a continuous improvement program," she says.

Soon, Medolac is going to bring out a new fortified milk product, which will compete with a very expensive 'human milk cream' sold by her former company, Prolacta. Medolac cannot say much about the product at this stage, but if it performs well and costs less than the $180 per ounce that Prolacta charges, it is likely to be well received. Milk fortified with human milk components (as opposed to cows milk components, in the most similar existing products), is intended to treat young infants in NICUs. Although a study showed that premature babies fed Prolacta's 'human milk cream' gained weight and length more quickly than those on a typical preemie diet [1], some hospitals report being unable to afford the product [2].

For all the very reasonable questions about affordability and moral quibbles around commoditizing human milk, breast milk-based products have a real potential to improve the health of infants who currently rely on formula. While infant formulas have improved over time, they can only add ingredients as science shows them to be important, and as such will logically always lag behind the real thing. As more research is done into the existing products, and as new ones appear on the market, the challenge will be to maintain biological functions in convenient formulations that hospitals, health insurers and parents can afford.

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