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This month's issue features vaccinated mothers transfer antibodies in milk to infants, dairy prevents falls and fractures, human milk cells, and dairy as part of a low-cost diet.

COVID-19 Vaccinated Mothers Transfer Active Antibodies in Milk to Infants

- **New research demonstrates that COVID-19 mRNA vaccines result in a robust response of milk antibodies specific to SARS-CoV-2.**
- **Lactating mothers that received mRNA vaccines produced milk with antibodies capable of neutralizing SARS-CoV-2, suggesting a protective effect for nursing infants.**
- **Because not all COVID-19 vaccines result in a robust milk immune response, breastfeeding mothers should be advised which vaccines offer the best protection for them and their nursing infant.**

Many U.S. parents breathed a sigh of relief in the fall of 2021 when the Pfizer-BioNtech COVID-19 vaccine received emergency use authorization for anyone five years and older. Although the youngest children are still ineligible for vaccination, infants—who are particularly vulnerable because of their immature immune systems—have access to another source of immune protection: human milk.

Human milk antibodies (also called immunoglobulins) are known to reduce the risk of infection and infection-related mortality in infants, so it is no surprise that they have been the subject of intense research during the COVID-19 pandemic. Early studies on milk from COVID-19 vaccinated mothers detected SARS-CoV-2-specific immunoglobulins [1, 2], offering promise that vaccinated mothers could transfer immunity to nursing infants. Now, a handful of new research [3-6] demonstrates that mRNA vaccination during lactation results in a robust immune response including milk immunoglobulins capable of neutralizing SARS-CoV-2.

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All studies measured the milk antibody response, specifically immunoglobulin G (IgG) and immunoglobulin A (IgA), before mRNA vaccination, after dose one, and after dose 2 (with the longest follow-up at three months after dose 2) [3]. The sharpest rise in both IgG and IgA titers specific to SARS-CoV-2 spike and receptor binding domain occurred after dose 2, with IgG as the dominant antibody present in 100% of samples [3-6]. Antibody concentrations did start to decline after three months, but IgG levels were still higher at this time point than in milk collected from mothers post-COVID-19 infection [3]. Additional studies beyond three months are needed to fully understand the persistence of milk antibodies after mRNA vaccination.

Both IgG and IgA from milk samples exhibited neutralization activity against SARS-CoV-2 [3, 6]. In one study, 60% of milk samples had neutralization activity as early as 18 days after the first vaccine dose, which increased to 85% of samples 18 days after the second dose [3]. In the other study that investigated antibody function, 100% of samples exhibited neutralization activity [6]. This neutralization activity was not as high as that recorded for milk from COVID-19 infected mothers [3], "but it is reasonable to assume that the high IgG [levels] in milk after vaccination have a protective effect for the infant," says human milk immunologist Dr. Rebecca Powell, Assistant Professor at the Icahn School of Medicine at Mount Sinai.

Although other vaccines, such as pertussis (whooping cough), were known to stimulate an active milk immune response, it wasn't a given that this would be the case with the COVID-19 vaccine. "The pandemic is science in real time," explains Powell. "We know that milk antibodies are there to protect offspring, and this is an evolved mechanism," says Powell, "but there is still so much about this we don't know. The pandemic has really opened up milk research."

One topic Powell hopes will draw more attention is whether other COVID-19 vaccines have a similar effect on milk immune factors as those using mRNA technology. "A huge shortcoming of the research has been the focus on Pfizer and Moderna, but there are so many other vaccines available globally," says Powell.

As a start, Powell and colleagues compared the milk antibody response between mRNA vaccines with the other FDA approved vaccine in the U.S., Johnson and Johnson/Janssen (J&J) [7]. They found a much less robust antibody response in milk from mothers receiving the J&J vaccine, including significantly lower levels of IgG antibodies specific to SARS-CoV-2 spike protein [7]. Keeping in mind the small number of study participants (n=13 J&J vaccine recipients, n=37 mRNA vaccine recipients), their results suggest mRNA vaccines result in better protection for infants compared with J&J [7].

This type of comparative research is not just of interest to scientists that study milk and passive immunity; it has direct implications for public health policy. Vaccination recommendations for breastfeeding mothers by national and global health authorities such as the Center for Disease Control (CDC) and World Health Organization (WHO) should consider a vaccine's potential to protect both mother and infant from infection. Outside the U.S., the most widely available vaccines are Astra-Zeneca/Oxford and several Chinese-manufactured vaccines (e.g., Coronavac), but it is not yet known if or how these vaccines influence the transfer of active antibodies into milk. As the pandemic enters its third year, there is clearly an urgent need to address these questions. "The lactating population should really be considered a special population when it comes to vaccines," says Powell. "We need to be able to tell them that their vaccine protects them, but also that they have good levels of antibodies in milk to protect their babies."

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Nutritional Intervention with Dairy Foods Prevents Falls and Fractures in Older Adults

- **Older adults are often malnourished, which can contribute to their increased risk of falls and fractures.**
- **A new study of more than 7000 residents of 60 aged-care facilities in Australia found that a nutritional intervention that increased the amount of dairy foods reduced the risk of falls and fractures.**
- **Participants in the intervention group receiving more dairy consumed, on average, higher protein and calcium than the control group on their usual diets.**
- **The findings suggest that nutritional interventions with dairy foods could serve as a public health measure for fracture prevention in aged care settings and potentially even in the broader community.**

We change in many ways as we grow old. In addition to external signs of aging such as white hair and wrinkles, our body also experiences less obvious changes, such as loss of muscle and bone mass.

These changes to muscle and bone are exacerbated by the fact that older individuals who need institutionalized care are often malnourished and lack adequate protein and calcium. This can in turn contribute to their increased risk of falls and fractures [1-4].

"My work was in aged care because their falls and fracture risk are the highest and their intake is the worst," says Dr. Sandra Iuliano of the University of Melbourne. "We wondered, can we have good clinical outcomes by just improving the food that they're eating?" she says.

When designing a nutritional intervention, Iuliano focused on dairy foods as they are a good low-cost source of protein and calcium and can be easily consumed by the elderly. "The reason we chose the dairy food group is because it's high in calcium and high in protein, and we were looking at falls and fracture reduction, so it was a natural kind of choice for us," she says. Previous research showed that consumption of milk, yogurt, and cheese, foods rich in calcium and protein, slows bone loss [5,6].

In a new study of 7195 residents of 60 aged-care facilities in Australia conducted over two years, Iuliano found that supplementation using high calcium, high protein dairy foods reduced the risk of falls and fractures [7]. The nutritional intervention was tailored to residents' preferences and consisted of regular retail milk, yogurt, and cheese incorporated into existing menus. "All we used is milk, yogurt and cheese, any combination, any fat content, and we looked at what the residents were eating and then enhanced what they were eating," says Iuliano.

The study found that the dairy foods nutritional intervention was associated with a 33% reduction in risk of fractures of any type, a 46% reduction in risk of hip fractures, and an 11% reduction in risk of falls relative to controls. "The risk reduction is a combination of fewer falls and less bone loss," says Iuliano. "All but one of the fractures resulted from a fall and we reduced falls, and if they don't fall, they're unlikely to fracture," she says.

Residents in facilities that received the dairy foods intervention maintained their bone and muscle to a greater extent than those in facilities that didn't receive the intervention. "There was deterioration in bone and muscle that we saw in the controls, but we didn't see that in the intervention group," says Iuliano. "That's probably the beauty of it, because the dairy had both the calcium and the high-quality protein, so we're doing two things at once with tackling muscle as well as tackling bone," she says.

There was no difference in all-cause mortality between the intervention and control groups, but the intervention does have the potential to improve quality of life. "They don't live longer, but they live fracture-free and potentially falls-free," says Iuliano.

Taking residents' preferences into account was important for compliance, a key to this kind of public health intervention. "Any intervention is only useful if there's good compliance, so the food has to taste good, and having foods they know and foods they like was the key," says Iuliano. "It's about what residents like, and how we can increase their dairy intake and put good choices in their diet," she says.

Dairy foods offered a lot of flexibility in how they could be incorporated into the facilities' menus, with both sweet and savory options. "All day we try to enable choices throughout the whole menu, so that way someone that doesn't eat breakfast cereal with milk, there's a choice somewhere else for them," says Iuliano. "Some places just loved cheese and they just ate cheese a lot, and other places we could fortify

milk and that doubled their intake just through the fortification, so it was very tailored to the facility and to the residents," she says.

The long-term nature of the study bodes well for introducing such interventions as public health policy. "Two years per facility, that's a long time, and the longevity shows that it can be sustainable," says Iuliano. "This is showing that this can be easily entrenched into policy and practice," she says.

Such food-based interventions could provide public health benefits at reasonable cost. "It's cost-effective," says Iuliano. "You're reducing the cost of a fracture, which is extremely expensive from a public health point of view, whereas the cost of the intervention, the food, wasn't expensive," she says.

Food-based interventions may also be more palatable than therapeutic interventions. "We're giving them foods that they know but they're gaining a clinical benefit from it, and it's like, I'd much rather have a piece of cheese than a tablet if I had to," she says.

Follow-up studies could combine dairy food interventions with other interventions such as exercise. "We might get an even better effect," says Iuliano. She also envisions similar interventions working in other parts of the world.

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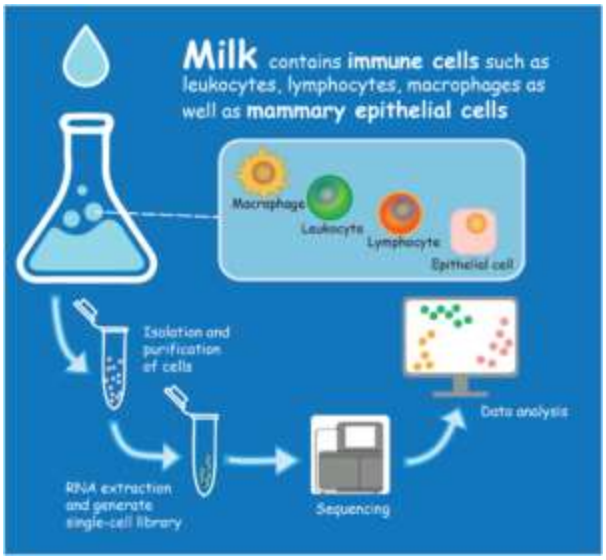
Exploring Cells in Human Milk with Single-Cell Sequencing

- **Scientists have applied single-cell RNA sequencing (scRNAseq) to little-understood human milk-derived cells, which will lead to a more detailed understanding of the different cell types and their function.**
- **The mammary epithelial cells studied were more heterogeneous than previously thought, with different types of cells producing fat, proteins, and carbohydrates and being in various stages of differentiation.**
- **The scRNAseq technique served as a proof-of-concept for future studies aimed at understanding how phenotypic factors, such as diabetes, in the mother can influence milk production.**

Milk is a complex mixture of nutrients, peptides, and immunological factors [1], yet very little is known about the cells within human milk that make it the ultimate nutritional source for developing infants. Now, scientists have developed a method for using RNA-sequencing to study these little-understood human milk cells [2]. This new technique using single-cell RNA sequencing (scRNAseq) sets the stage for future experiments that will gain an unprecedented understanding of human milk-derived cells and the intricacies of human lactation [2].



Graphic Art by Xuan He

"It's kind of a proof-of-concept. You can acquire highly detailed, useful information using this approach," says Michael Rudolph, a physiology professor at the University of Oklahoma who co-authored the first paper describing the scRNAseq technique [3]. "The key will be to apply this approach to begin testing hypotheses about maternal function." One of the primary purposes of applying scRNAseq to milk cells is to understand how factors like diabetes or metabolic disease might hamper lactation in some women [2].

Human milk contains a cocktail of different cell types. Less than 10% of the cells are thought to be immune cells, while the majority are cells that derive from the mammary epithelium and aid in milk synthesis [4]. Jayne Martin Carli, postdoctoral researcher at the University of Colorado and the lead author of the scRNAseq study [3], says researchers aren't entirely certain about the origin of these cells and how they end up in the milk, and research has been hindered by ethical and practical hurdles in accessing breast tissue from lactating mothers. Human milk samples can be used as a proxy for studying mammary function [3].

ScRNAseq is an advanced genetic technique that details each cell's individual transcriptome—a process that shows what genes are active in each cell. By applying scRNAseq to human milk-derived cells, researchers can gain novel insights into the different kinds of cells found in human milk and their function. With this approach, researchers can also potentially glean insights on the physiological reasons behind why some women have difficulty producing milk [2]. "We already had broad stores of knowledge of cells that were already there but now we have a much more detailed picture," explains Martin Carli.

Martin Carli and her co-authors took milk samples from two women with similar BMIs at two weeks post-partum. The samples were centrifuged to collect and isolate the cells, and cryopreserved to arrest the cells in development. Dead cells were identified through staining and removed using a technique called fluorescence-activated cell sorting. The research team analyzed a total of 3740 cells from the samples that were sequenced and characterized [3]. "Once you have your sequencing data it then becomes an exercise in bioinformatics," explains Rudolph.

Rudolph says he was surprised by the heterogeneity of the cells. "Going in to this I thought it was going to be mostly one particular cell type and that it would be fully functionally differentiated," he says. "We identified unique populations of cells that may individually contribute to lactation as more of a symphony—it's a bunch of individual types of cells that cumulatively contribute to manufacturing individual components of the milk, whether its milk protein, fat, or carbohydrates. They seem to have important and individual features that contribute to making milk."

Additionally, the research team found cells that were in various stages of differentiation. Some of the cells expressed genes associated with progenitor cells, whereas others expressed genes that suggested they were at later stages of maturity [3]. Previous literature suggested the presence of stem cells within human milk [5, 6], but the scRNAseq technique used by Martin Carli was not able to detect any [3].

Whereas the paper published by Martin Carli et al. in the *Journal of Mammary Gland Biology and Neoplasia* [3] was the first to describe this method, subsequent lab groups have also used this technique with similar results [7, 8]. scRNAseq has also been applied to cow's milk [9, 10].

Research done by Martin Carli and co-authors gathered a baseline understanding of milk-derived cell heterogeneity, and it represents just the beginning for a wide array of potential research questions using the scRNAseq method. She is focused on studying factors that affect milk insufficiency. "I'm trying to

understand how women with diabetes during pregnancy have a harder time making milk for their babies," she says.

"I'm interested in the mechanics of how things end up affecting the milk composition," says Rudolph, who gave the example of maybe studying a mother that has COVID-19, and asking what immune cells might appear in her milk.

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Milk and Other Animal-sourced Foods May Be Key Components of a Low-cost Nutritious Diet

- **There has been much debate about the respective roles of plant- and animal-sourced foods in environmentally sustainable diets, but few studies have taken both nutritional content and cost into account.**
- **A pair of recent studies modeled the role of plant- and animal-sourced foods in developing a least-cost nutritious diet in the United States and New Zealand.**
- **The researchers found that nutritious diets including both animal- and plant-based foods were considerably cheaper than those consisting exclusively of plant-based foods, and these diets also included a large amount of milk.**

From steak and salad to milk and cereal, people enjoy a wide variety of foods from both plant and animal sources. As researchers have studied the environmental sustainability of various diets, there has been much debate about the respective roles of plant- and animal-sourced foods in such diets [1,2].

Two recent studies approach this question from an economic perspective by taking into account both the nutritional content and monetary cost of foods. "Our starting point was to find out what foods could be included for the cheapest diet possible," says Dr. Sylvia Chungchunlam of the Riddet Institute in New Zealand, who was the first author on both studies [3,4]. "Then we wanted to see what would happen if we actually went to a plant-only based diet and how that would affect the cost of the diet," she says.

The researchers used a type of analysis known as linear programming to identify the combination of foods that could meet all the nutrient requirements of a

healthy adult at the lowest cost [5]. Foods from animal sources are particularly rich in several important nutrients, including protein, essential amino acids, vitamins and minerals [6]. As a result, the researchers tested whether animal-based foods would be present in their least-cost modelled diets, and how this diet would compare with plant-based diets.

In their initial study, Chungchunlam and her colleagues focused on the United States [3]. "We decided to go with a US study just to have a broad picture of what's happening in the developed world," says Chungchunlam. They used food composition data from 2016 and national food prices from 2009–2010 in their analysis, the most up-to-date comprehensive data available [7,8].

The researchers found that animal-based foods such as milk, eggs, fish and meat were included in the diet that met the energy and nutrient requirements of healthy adults at the lowest cost. "What we showed was that the cheapest diet possible included animal-sourced foods," says Chungchunlam. "If we wanted to model a plant-based diet, that was 40% more in terms of cost," she says.

The least-cost diet contained a large amount of milk, suggesting that dairy was particularly cost-effective at meeting nutritional requirements. "Dairy is a good vehicle for fortification and dairy is actually quite cheap, and so dairy would always tend to come into those model diets, and most of the time dairy is very culturally acceptable," says Chungchunlam.

Of course, food prices vary from country to country, and the amounts of animal-sourced foods required to achieve a least-cost nutritious diet could vary accordingly. Given that their initial study pertained only to US food prices and took into account US government subsidies on animal-based foods, Chungchunlam and her colleagues decided to perform a follow-up study in New Zealand, which has similar eating patterns as the US but lacks similar subsidies [4]. "We wanted to see if there was a similar effect where there was not as much government subsidies in animal-based products," says Chungchunlam.

Similar to the US study, the New Zealand study also found that foods of animal origin, such as milk, eggs, and green mussels, were required in the least-cost dietary pattern that met adult nutritional requirements. "We found that the plant-based diet was still 34% more expensive," says Chungchunlam.

These results suggest that at least in developed countries, the least-cost dietary pattern that meets nutritional requirements may rely on foods sourced from both plants and animals. "Our next step would probably look at developing countries because the price of animal-sourced foods in developing countries is actually much higher compared with plant-based or cereal-based diets," says Chungchunlam.

The researchers do note that their studies are economic analyses that are limited to the effect of food costs on achieving a baseline level of nutrition, and that the resulting dietary patterns have not been optimized for other features. "We're not telling people not to have a plant-based diet, that's their choice, they just have to be aware that it will cost more," says Chungchunlam. "What we're also saying is to look at which nutrients might become first-limiting if you make that shift towards those plant-based diets," she says.

The results of the two studies suggest that animal-based foods, and particularly dairy, may be crucial for meeting nutritional requirements at the lowest cost. "When considering which foods we should include to meet nutrient requirements, the lowest cost diet needs animal foods, it needs milk, it needs eggs, and it needs fish or seafood," says Chungchunlam. "So the least-cost diet needs animal-sourced foods to be present," she says.

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