Studying zinc increases understanding of obesity, breast cancer

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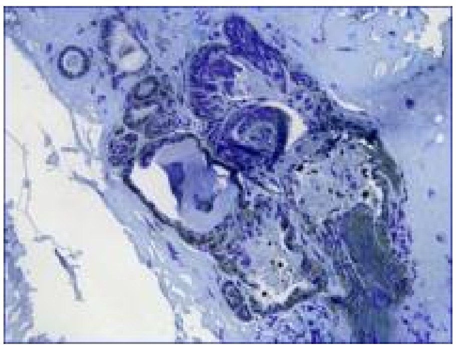

Cross section of a cancerous human breast tissue. The black in the slide is ZnT2, a zinc transporter, indicating a high quantity of zinc in this cell. Image: Shannon Kelleher

(PhysOrg.com) -- The human body loves zinc. In fact, without zinc, humans wouldn't be able to grow, make babies, feed babies or fight diseases; over 300 biological functions in the human body rely upon zinc. Too much or too little zinc and processes suffer, stressing our bodies and making us vulnerable to diseases and possibly early death. Even though zinc is incredibly important for our survival, our current understanding is very limited. Only a handful of researchers across the world work on the biology of zinc at the molecular level, how it operates within our cells and ultimately how our bodies make use of it. One of those few groups of zinc researchers works in Penn State's Department of Nutritional Sciences.

Under the guidance of Shannon Kelleher, assistant professor of nutritional sciences, a cohort of research and postdoctoral scientists along with graduate and undergraduate students perform research on zinc that is funded by several agencies, including the National Institutes of Health and the Department of Defense. Their work consists, primarily, of discovering how zinc interacts with our bodies, specifically when it comes to reproduction. They ask questions such as, “Once zinc is in our body, where does it go, what does it do, and how does it do it?" They perform controlled experiments involving certain “zinc transporters” -- proteins our bodies create to help move zinc around. Much like a host of trained athletes who pass the Olympic flame from Athens, Greece, to the site of the Olympics every few years, so, too, do specific proteins created by the body pass zinc atoms from the digestive system to all cells throughout the body.

There are 24 of these zinc transporters and each has its own purpose: some move zinc into a cell, some carry it around inside the cell and some push zinc out of cells. Understanding what the body does with zinc (aside from looking for zinc atoms) requires understanding how zinc is transported in individual cells. That’s partly what the work in Kelleher’s lab consists of -- mapping the journeys of one little (but important) mineral and discovering how it functions in our bodies. Kelleher’s research studies zinc’s impact at all stages of life, from old age to infancy and even before birth.

Breast Cancer, Obesity in Older Women

For some reason, postmenopausal women who are obese are at a higher risk for breast cancer, compared to postmenopausal women who are not obese. Researchers also know that estrogen plays a role in this relationship, which explains the postmenopausal part of the equation (women’s estrogen levels typically decrease as the result of menopause). It doesn’t explain how estrogen and obesity are related to breast cancer, though. That's what Kelleher and her colleagues are trying to find out.

"When you're obese, the fat cells in your body have expanded," said Kelleher. "Obesity promotes an inflammatory response, and we know that women with inflammatory diseases are at a higher risk of breast cancer." Kelleher is trying to make a cohesive picture of the factors involved: women, menopause, zinc, estrogen and breast cancer, with the ultimate goal of being able to prevent or better fight breast cancer in the future.

Her first experiment, which she is conducting now, is to find out which zinc transporters change when a normal breast cell becomes a tumor. This work is an extension of her observation that breast cancer cells have high levels of zinc compared to non-cancerous breast cells. That observation prompted researchers with a conundrum reminiscent of the chicken-or-egg dilemma: they are not sure if breast cancer causes cells to accumulate higher levels of zinc, or if the higher levels of zinc are the result of another process that also caused the breast cancer. What is known, however, is that the two are related. Using this knowledge, Kelleher is devising more studies that could leverage zinc's travels in a way that will improve the health of people who have breast cancer.

The Infant Immune System and Milk

Once out of the womb, infants are exposed to a mass of new diseases. They need a reliable immune system to survive and one key component of the immune system is zinc. Zinc deficiency has been cited by the World Health Organization as most common cause of disease in children under the age of 5 worldwide. Roughly one-third of the world's population suffers from some degree of zinc deficiency and in some areas of the world, 75 percent of the population is zinc deficient (women and children are more likely to have a deficiency).

Zinc not only helps bolster the immune system, but it is necessary for growth. If there are low levels of zinc in breast milk that is nourishing a baby, the infant will be affected significantly. Common results of prolonged zinc deficiency in infants include increased infections, skin disorders and behavioral and developmental problems. This could be one of the reasons that breast milk contains very high levels of zinc -- in a way, it fuels the baby's growth and development.

Research in Kelleher's lab focuses on what the mammary gland does with zinc, how it gets in, where it's stored within cells and how the mammary gland moves it into milk. The researchers use fluorescent dyes that change color when attached to zinc in specific parts of the cells: one dye turns red when attached to zinc in the cell's mitochondria, another dye turns green when attached to zinc in the cell's vesicles. They've already figured out which transporters are responsible for moving zinc into milk and they are currently trying to understand how it first gets in and where it goes.

Through this process of molecular cartography, Kelleher and her colleagues are laying the groundwork for future research. After they know where zinc goes and how it gets there, scientists can step in and use this to their advantage, reducing some of the more serious side effects of zinc deficiency.

A Necessity Before Birth

Zinc plays a huge role even as humans develop in the womb. The placenta nourishes the developing baby and the development of a placenta during pregnancy is directly related to zinc levels in a woman's body. Placenta cells attach to the uterine lining during the initial stages of pregnancy; in doing so, they are invading the uterine cells, breaking them apart so that the developing fetus can attach. Placenta cells are like "chewing machines," said Kelleher. And what do placenta cells rely on for this chewing ability? Zinc.

It’s not as gruesome as it sounds, though. The placenta is important for supplying blood to a growing fetus. The most efficient and effective way to do this is to have an incredibly tight connection to the uterine lining. Low zinc levels could mean less efficient “chewing” and a looser connection between uterus and placenta. Ultimately this could lead to preterm labor or pre-eclampsia (a condition that involves high blood pressure), two outcomes that put both mother and baby in danger.

Kelleher and her colleagues are working to understand which zinc transporters play a role in placental development, and, in situations where the placenta poses a threat to both mother and baby, what can be done to improve the outcome.

Mobility and Fertility

Zinc affects us even further back in our growth than the womb stage: as a sperm. Zinc is essential for reproductive fertility. It helps sperm on their way to starting the reproductive process. Without zinc, sperm loses its chances of ‘breaking into’ an egg. Also, sufficient zinc levels boost sperm’s mobility, allowing it to become a “strong swimmer,” said Kelleher.

Like breast cancer, both prostate and testicular cancers have abnormal zinc levels. Like milk, prostate fluid contains very high levels of zinc, too. “Nobody knows why prostate fluid is high in zinc,” said Kelleher, “but we do know that the prostate intentionally secretes zinc into the fluid.” Currently, Kelleher is looking at mild zinc deficiency and how that impacts fertility in mice.

New Ways to See Zinc

While it is important to know the effects of zinc deficiency and how zinc impacts the body, it is also important to know how to determine if the body is zinc-deficient.

One of the most common ways to measure zinc levels in the body is by looking at blood plasma. However, only a severe zinc deficiency will show up on these tests. Because even a minor zinc deficiency can affect a person's growth, cognition and immune system, these tests fall short of diagnostic needs.

Kelleher has devised a new system for measuring zinc, which she is testing now. She is looking at changes in gene expression in white blood cells. White blood cells, which are part of the body's immune system, use zinc when "expressing" certain genes (Most genes can be thought of as blueprints for a building -- they contain information that can be used to build a structure. When a gene is "expressed," it means that the blueprint has been read and the building process has begun. In the case of the gene, the result of this building process is usually a protein.).

In many cases, a gene is expressed in response to some condition the body is experiencing. When you get a cut, for example, your body will usually begin a chain reaction to eventually create a scab that stops the flow of blood. A change in gene expression sets off the process of making a scab. If you had a way of looking at changes in all the genes that are expressed at one time (which Kelleher does: a process called microarrays), you could monitor the levels of gene expression when an organism is at varying levels of zinc deficiency. The genes that change their expression are the ones affected by zinc deficiency.

Although there are over 35,000 genes that can be expressed in mice, Kelleher has her target gene audience narrowed down to about 20. One (or all) of those could be an indicator for low zinc in the body.

As they chart more of where zinc travels and figure out new ways to precisely measure it in the body, Kelleher and her colleagues are increasing a worldwide understanding of zinc. Their research today could be used to remedy the maladies that follow even marginal zinc deficiency.

Provided by Pennsylvania State University

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