Medical Xpress

Zinc helps against infection by tapping brakes in immune response

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New research suggests that zinc helps control infections by gently tapping the brakes on the immune response in a way that prevents out-of-control inflammation that can be damaging and even deadly.

Scientists determined in human cell culture and animal studies that a protein lures zinc into key cells that are first-responders against infection. The zinc then interacts with a process that is vital to the fight against infection and by doing so helps balance the immune response.

This study revealed for the first time that zinc homes in on this pathway and helps shut it down, effectively ensuring that the immune response does not spiral out of control. The team led by Ohio State University researchers also found that if there is not enough zinc available at the time of infection, the consequences include excessive inflammation.

In this research, zinc's activity was studied in the context of sepsis, a devastating systemic response to infection that is a common cause of death in intensive-care unit patients. But scientists say these findings might also help explain why taking zinc tablets at the start of a common cold appears to help stem the effects of the illness.

"We do believe that to some extent, these findings are going to be applicable to other important areas of disease beyond sepsis," said Daren Knoell, senior author of the study and a professor of pharmacy and internal medicine at Ohio State. "Without zinc on board to begin with, it could increase vulnerability to infection. But our work is focused on

what happens once you get an infection – if you are deficient in zinc you are at a disadvantage because your defense system is amplified, and inappropriately so.

"The benefit to health is explicit: Zinc is beneficial because it stops the action of a protein, ultimately preventing excess inflammation."

While this study and previous work linking zinc deficiency to inflammation might suggest that supplementation could help very sick ICU patients, it's still too early to make that leap.

"I think the question is whom to give zinc to, if anybody at all. We predict that not everybody in the ICU with sepsis needs zinc, but I anticipate that a proportion of them would," Knoell said. "Zinc is a critical element that we get from our diet, but we do not think we can give zinc and fix everything. Usually, if there is zinc deficiency, we would expect to see other nutrient deficiencies, too."

Zinc deficiency affects about 2 billion people worldwide, including an estimated 40 percent of the elderly in the United States – who are also among the most likely Americans to end up in an ICU.

The research is published in the journal *Cell Reports*.

Knoell's lab previously showed that zinc-deficient mice developed overwhelming inflammation in response to sepsis compared to mice on a normal diet. Zinc supplementation improved outcomes in the zinc-deficient mice.

Until now, the beneficial effects of zinc in combating infection have not been fully understood at the molecular level. This is because zinc has numerous complex jobs in the body and interacts with thousands of proteins to sustain human life. Of all the zinc contained in our bodies,

only about 10 percent of it is readily accessible to help fight off an infection, said Knoell, also an investigator in Ohio State's Davis Heart and Lung Research Institute.

"We believe that our findings help to narrow an important gap that has existed in our understanding of how this relatively simple metal helps us defend ourselves from infection," he said.

In this work, Knoell and colleagues sought to zero in on zinc's role in preventing the inflammation that had led to such poor outcomes in the zinc-deficient mice.

In experiments using human monocytes – cells involved in the first line of defense against an invading pathogen – the researchers examined what happens when the immune response is launched.

When a pathogen is recognized, a series of molecules wake up from dormancy to create a process that activates the innate immune response. A major part of this process involves the NF-κB pathway, named for a highly active protein that is known to play an important role in the immune response to infection. Once NF-κB is activated and enters the nucleus, a gene is expressed that produces a zinc transporter called ZIP8. The transporter then rapidly mobilizes to the cell's wall, where it can then shuttle zinc from the bloodstream into the cell.

After cell entry, zinc is then directed to and binds to a different protein in the NF-kB pathway. When this happens, it halts any further activity in that process. The cumulative impact of this feedback loop is that it prevents excessive inflammation, which can be damaging to cells and the body.

"The immune system has to work under very strict balance, and this is a classic example of where more is not always better," Knoell said. "We

want a robust inflammatory response, which is part of our natural programming to defend us against a bug. But if that is unchecked, and there is too much inflammation, then it not only attacks the pathogen but can also cause much more collateral damage."

The researchers knew from previously published experiments that if ZIP8 activation was prevented, zinc couldn't come into the cell and the cells died. In the current study, collaborators who specialize in computational modeling of protein interactions helped identify the likely target of zinc once it enters the cell: specific binding sites on a protein called IKKB. When researchers allowed this protein to function unchecked in mice with zinc deficiency, the animals developed excessive inflammation in response to sepsis – confirmation that IKKB was zinc's target to turn off the inflammatory pathway.

"There are certainly other zinc targets in the cell, but we found evidence that zinc is brought in by ZIP8 to turn the pathway off by interacting with this protein at a specific region," Knoell said.

The recommended daily allowance for zinc ranges from 8 to 11 milligrams for most adults. Red meat and poultry provide the majority of zinc in the American diet, according to the National Institutes of Health. Other food sources include beans, nuts, some shellfish, whole grains, fortified cereals and dairy products. The nutrient is also available in supplement form. Knoell said it is possible but relatively uncommon to take in too much zinc to reach toxic levels.

His lab is continuing to study the NF-κB pathway, inflammation and zinc deficiency in other disease processes. And though zinc would be inexpensive and easy to take as a supplement, Knoell said many questions remain about whether zinc should be considered as an intervention for specific disorders.

"There might be therapeutic implications about giving supplemental zinc in a strategic manner to help improve some people with certain conditions. But also, could we learn from this so someday we can be more diagnostic about who it is that needs zinc? And if so, what dose and for how long?" he said.

Provided by The Ohio State University

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