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Key feature of immune system survived in humans, other primates for 60 million years

CORVALLIS, Ore. – A new study has concluded that one key part of the immune system, the ability of vitamin D to regulate anti-bactericidal proteins, is so important that is has been conserved through almost 60 million years of evolution and is shared only by primates, including humans – but no other known animal species.

The fact that this vitamin-D mediated immune response has been retained through millions of years of evolutionary selection, and is still found in species ranging from squirrel monkeys to baboons and humans, suggests that it must be critical to their survival, researchers say.

Even though the "cathelicidin antimicrobial peptide" has several different biological activities in addition to killing pathogens, it's not clear which one, or combination of them, makes vitamin D so essential to its regulation.

The research also provides further evidence of the biological importance of adequate levels of vitamin D in humans and other primates, even as some studies and experts suggest that more than 50 percent of the children and adults in the U.S. are deficient in "the sunshine vitamin."

"The existence and importance of this part of our immune response makes it clear that humans and other primates need to maintain sufficient levels of vitamin D," said Adrian Gombart, an associate professor of biochemistry and a principal investigator with the Linus Pauling Institute at Oregon State University.

In a new study in the journal *BMC Genomics*, researchers from OSU and the Cedars-Sinai Medical Center describe the presence of a genetic element that's specific to primates and involved in the innate immune response. They found it not only in humans and their more recent primate ancestors, such as chimpanzees, but also primates that split off on the evolutionary tree tens of millions of years ago, such as old world and new world primates.

The genetic material – called an Alu short interspersed element – is part of what used to be thought of as "junk DNA" and makes up more than 90 percent of the human genome. That genetic material, however, is now understood to often play important roles in regulating and "turning on" the expression of other genes.

In this case, the genetic element is believed to play a major role in the proper function of the "innate" immune system in primates – an ancient, first line of defense against bacteria, viruses and other pathogens, in which the body recognizes something that probably doesn't belong there, even though the specific pathogen may never have been encountered before.

"Many people are familiar with the role of our adaptive immune system, which is what happens when we mount a defense against a new invader and then retain antibodies and immunity in the future," Gombart said. "That's what makes a vaccine work. But also very important is the innate immune system, the almost immediate reaction your body has, for instance, when you get a cut or a skin infection."

In primates, this action of "turning on" an optimal response to microbial attack only works properly in the presence of adequate vitamin D, which is actually a type of hormone that circulates in the blood and signals to cells through a receptor. Vitamin D is produced in large amounts as a result of sun exposure, and is available in much smaller amounts from dietary sources.

Vitamin D prevents the "adaptive" immune response from over-reacting and reduces inflammation, and appears to suppress the immune response. However, the function of the new genetic element this research explored allows vitamin D to boost the innate immune response by turning on an antimicrobial protein. The overall effect may help to prevent the immune system from overreacting.

"It's essential that we have both an innate immune response that provides an immediate and front

line of defense, but we also have protection against an overreaction by the immune system, which is what you see in sepsis and some autoimmune or degenerative diseases," Gombart said. "This is a very delicate balancing act, and without sufficient levels of vitamin D you may not have an optimal response with either aspect of the immune system."

After years of research, scientists are continuing to find new roles that vitamin D plays in the human body. It can regulate the actions of genes that are important to bone health, calcium uptake, and inhibition of cell growth. It helps regulate cell differentiation and, of course, immune function.

"The antimicrobial peptide that we're studying seems to be involved not just in killing bacteria, but has other biological roles," Gombart said. "It recruits other immune cells and sort of sounds the alarm that something is wrong. It helps promote development of blood vessels, cell growth and healing of wounds. And it seems to have important roles in barrier tissues such as skin and the digestive system. Vitamin D is very important for the health of the skin and digestive system, and putting the cathelicidin antimicrobial peptide gene under its regulation may be important in this function."

Any one, or some combination of those biological roles may be why vitamin D-mediated regulation of the antimicrobial peptide has been conserved in every primate species ever examined for its presence, researchers said, and did not disappear long ago through evolutionary variation and mutation. The evolution of primates into many different families and hundreds of species has been carefully tracked through genetic, molecular sequence and fossil studies, but the presence of this regulatory element in primates is still largely the same as it's been for more than 50 million years.

The evolutionary survival of this genetic element and the placement of the cathelicidin antimicrobial peptide gene under the regulation of the vitamin D pathway "may enable suppression of inflammation while potentiating innate immunity, thus maximizing the overall immune response to a pathogen and minimizing damage to the host," the researchers wrote in their conclusion.

Vitamin D deficiency is an issue of growing concern among many scientists, due to changing lifestyle or cultural trends in which many people around the world get less sun exposure and often inadequate dietary levels of the vitamin. It's a special problem with the elderly, which often have reduced exposure to sunlight and less ability to produce vitamin D in their skin – and at least partly as a result, are more susceptible to bone fractures, chronic inflammation and infectious disease.

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