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Research suggests a new strategy to prevent or halt periodontal disease

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Periodontitis, a form of chronic gum disease that affects nearly half of the U.S. adult population, results when the bacterial community in the mouth becomes unbalanced, leading to inflammation and eventually bone loss. In its most severe form, which affects 8.5 percent of U.S. adults, periodontitis can impact systemic health.

By blocking a molecular receptor that bacteria normally target to cause the disease, scientists from the University of Pennsylvania have now demonstrated an ability in a mouse model to both prevent periodontitis from developing and halt the progression of the disease once it has already developed.

The study, published in the Journal of Immunology, was led by Toshiharu Abe, a postdoctoral researcher in the Department of Microbiology in Penn's School of Dental Medicine. Abe works in the lab of George Hajishengallis, a professor in the department who was a senior author on the paper. The co-senior author was John D. Lambris, the Dr. Ralph and Sallie Weaver Professor of Research Medicine in the Department of Pathology and Laboratory Medicine in Penn's Perelman School of Medicine. Kavita B. Hosur and Evlambia Hajishengallis from Penn Dental Medicine also contributed to the research, as did Penn Medicine's Edimara S. Reis and Daniel Ricklin.

In previous research, Hajishengallis, Lambris and colleagues showed that Porphyromonas gingivalis, the bacterium responsible for many cases of periodontitis, acts to "hijack" a receptor on white blood cells called

C5aR. The receptor is part of the complement system, a component of the immune system that helps clear infection but can trigger damaging inflammation if improperly controlled.

By hijacking C5aR, P. gingivalis subverts the complement system and handicaps immune cells, rendering them less able to clear infection from the gum tissue. As a result, numbers of P. gingivalis and other microbes rise and create severe inflammation. According to a study published last year by the Penn researchers, mice bred to lack C5aR did not develop periodontitis.

Meanwhile, other studies by the Penn group and others have shown that Toll-like receptors, or TLRs—a set of proteins that also activate immune cell responses—may act in concert with the complement system. In addition, mice lacking one form of TLR called TLR2 do not develop bone loss associated with periodontitis, just like the C5aR-deficient mice.

In the new study, the Penn team wanted to determine if the synergism seen by other scientists between the complement system and TLRs was also at play in this inflammatory gum disease.

To find out, they injected two types of molecules, one that activated C5aR and another that activated TLR2, into the gums of mice. When only one type of molecule was administered, a moderate inflammatory response was apparent a day later, but when both were injected together, inflammatory molecules increased dramatically—soaring to levels higher than would have been expected if the effect of activating both receptors was merely additive.

This finding suggested to the scientists that the Toll-like receptor signaling was somehow involved in "crosstalk" with the complement system, serving to augment the inflammatory response. Turning that

implication on its head, they wondered whether blocking just one of these receptors could effectively halt the inflammation that allows P. gingivalis and other bacteria to thrive and cause disease.

Testing this hypothesis, the researchers synthesized and administered a molecule that blocks the activity of C5aR, to see if it could prevent periodontitis from developing. They gave this receptor "antagonist," known as C5aRA, to mice that were then infected with P. gingivalis. The C5aRA injections were able to stave off inflammation to a large extent, reducing inflammatory molecules by 80 percent compared to a control, and completely stopping bone loss.

And when the mice were given the antagonist two weeks after being infected with P. gingivalis, the treatment was still effective, reducing signs of inflammation by 70 percent and inhibiting nearly 70 percent of periodontal bone loss.

"Regardless of whether we administered the C5a receptor antagonist before the development of the disease or after it was already in progress, our results showed that we could inhibit the disease either in a preventive or a therapeutic mode," Hajishengallis said.

This is significant for extending these findings to a potential human treatment, as treatments would most likely be offered to those patients already suffering from gum disease.

Because not all cases of periodontitis are caused by P. gingivalis, the research team also wanted to see whether C5aRA could effectively prevent or treat the disease when it arose due to other factors. To do so, they placed a silk ligature around a single molar tooth in a group of mice. The obstruction not only blocked the natural cleaning action of saliva, but also enabled bacteria to stick to the ligature itself, resulting in a massive accumulation of bacteria. This microbial build-up rapidly leads

to periodontitis and bone loss, within just five days in the mice.

The researchers then injected the gum tissue adjacent to the ligated molar tooth with C5aRA in some of the mice, and gave the other mice a control.

"These mice that got the C5a receptor antagonist developed at least 50 percent less inflammation and bone loss compared to an analog of C5a receptor antagonist which is not active," Hajishengallis said.

This result gives the researchers greater confidence that the C5aRA treatment could be effective against periodontitis in general, not just those cases caused by P. gingivalis bacteria.

The team is now working to replicate their success in mice in other animal models, an important step toward extending this kind of treatment to humans with gum disease.

"Our ultimate goal is to bring complement therapeutics to the clinic to treat periodontal diseases," Lambris said. "The complement inhibitors, some of which are in clinical trials, developed by my group are now tested in various periodontal disease animal models and we hope soon to initiate clinical trials in human patients."

Provided by University of Pennsylvania