Researchers reverse bone loss in immune disorder

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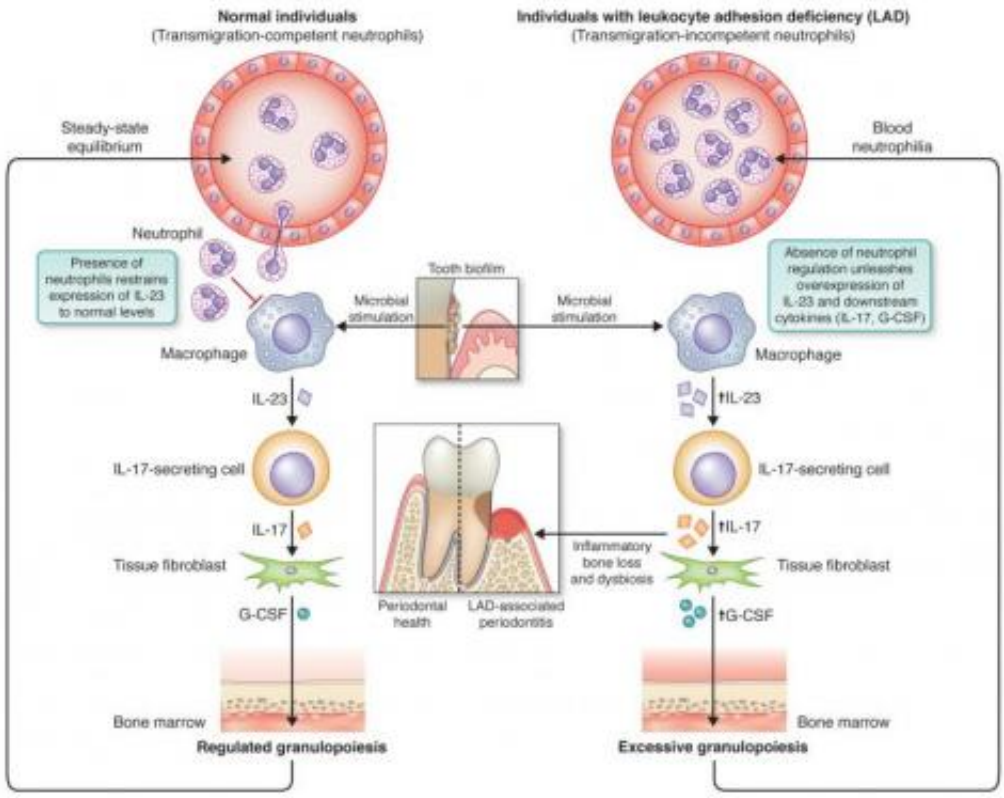

The absence of recruited neutrophils to the periodontal tissue in LAD patients leads to unrestrained local production of IL-23 and hence IL-17 and G-CSF. Increased IL-17 leads to inflammatory bone loss and dysbiosis, whereas increased G-CSF leads to excessive release of mature neutrophils from the bone marrow. In contrast, normal recruitment of neutrophils regulates the expression of the same cytokines maintaining homeostasis in terms of periodontal health and release of mature neutrophils from the bone marrow. Credit: Copyright Niki Moutsopoulos and George Hajishengallis

Patients with leukocyte adhesion deficiency, or LAD, suffer from frequent bacterial infections, including the severe gum disease known as periodontitis. These patients often lose their teeth early in life.

New research by University of Pennsylvania School of Dental Medicine researchers, teaming with investigators from the National Institutes of Health, has demonstrated a method of reversing this bone loss and inflammation.

The work was led by Penn Dental Medicine's George Hajishengallis, professor in the Department of Microbiology, in collaboration with Niki Moutsopoulos of the National Institute of Dental and Craniofacial Research. It was published in the journal *Science Translational Medicine*.

Leukocyte adhesion deficiency is a rare but life-threatening disease. Patients can succumb to bacterial infections because their immune systems lack a molecule required by immune cells, specifically neutrophils, to go to the site of infection.

Researchers used to believe that LAD patients developed severe periodontitis because of this inability of neutrophils to cross from the bloodstream into gum tissue. Bacteria, therefore, were believed to thrive unchecked in the gums.

"Because this view was so reasonable, nobody had questioned it," Hajishengallis said.

The new study challenges this assumption.

The team led by Hajishengallis and Moutsopoulos noticed that gum disease and bone loss continued unchecked even when LAD patients were given antibiotics or had their plaque removed. As expected, the LAD patients did not have neutrophils in their gum tissue, only in the

bloodstream. Looking more closely, however, they realized that these patients had abundant bacteria on the surface of their teeth but normal bacterial levels inside their gums.

"This is a very different form of periodontitis than we see in otherwise healthy people, in which the neutrophils can cause disease by being too active or present at high numbers in the gums," Hajishengallis said.

To understand what was unique about the LAD patients' disease, the researchers examined their immune system-related genes and proteins. Compared to people with periodontitis or gingivitis who were otherwise healthy, one molecule in particular stood out: people with LAD had very high levels of IL-17 mRNA and IL-17-expressing cells in their gum tissue.

These findings matched up with what the researchers had observed in mice that were bred to lack LFA-1, a molecule that normally helps neutrophils exit the bloodstream. Like human LAD patients, these mice had serious periodontal disease early in life, and their gums contained high levels of IL-17 mRNA and protein, as well as IL-23, a protein in the same pathway as IL-17.

IL-17 is in a signaling pathway that acts as a feedback loop for the immune system. When the pathway senses that a tissue contains few neutrophils, levels of IL-23 and IL-17 go up, encouraging more neutrophil production and migration from the bloodstream into the tissue. But, because LAD patients' neutrophils cannot move into the tissue, this pathway goes awry, leading to inflammation.

Not only can IL-17 encourage inflammation, but it can also encourage the development of osteoclasts, cells that break down bone, in this case teeth.

"We suspected that the bone loss was occurring because of IL-17 and not because the neutrophils could not control the bacterial infection," Hajishengallis said.

To determine whether IL-17 or IL-23 was to blame for the periodontitis and bone loss in the mice with the LAD-like disease, the researchers injected molecules that block these proteins' activity in their gums.

"We found out that by blocking these two, not only do we inhibit inflammation and bone loss, but we also inhibit the bacterial overgrowth," Hajishengallis said. "This is not as strange as it might sound. Periodontal bacteria thrive on inflammation. Consuming the breakdown products of tissues is how they get their food. So if you inhibit inflammation you starve them."

The authors said that this result suggests that the reason bacterial numbers are so high in these mice, and, by extension, human LAD patients, is not because of a defect in the immune system's surveillance mechanism but because of the inflammation caused by the immune system's abnormal response to normal levels of bacteria in the gums.

"So in other words the bacterial overgrowth is the result and not the cause of this type of periodontitis," Hajishengallis said.

Molecules that target and inhibit the activity of IL-17 are already used to treat autoimmune diseases such as psoriasis and rheumatoid arthritis, so the researchers want to see whether these compounds could also be used to treat periodontitis in LAD patients.

More information: "Defective Neutrophil Recruitment in Leukocyte Adhesion Deficiency Type I Disease Causes Local IL-17–Driven Inflammatory Bone Loss," by N. Moutsopoulos et al. *Science Translational Medicine*, 2014.