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Researchers identify protein involved in causing gum disease, osteoporosis, arthritis

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Investigators at Hospital for Special Surgery, collaborating with researchers from other institutions, have contributed to the discovery that a gene called interferon regulator factor-8 (IRF-8) is involved in the development of diseases such as periodontitis (gum disease), rheumatoid arthritis and osteoporosis. The study, which will be published online August 30, ahead of print, in the journal *Nature Medicine*, could lead to new treatments in the future.

"The study doesn't have immediate therapeutic applications, but it does open a new avenue of research that could help identify novel therapeutic approaches or interventions to treat diseases such as periodontitis, rheumatoid arthritis or osteoporosis," said Baohong Zhao, Ph.D., lead author of the study and a research fellow in the Arthritis and Tissue Degeneration Program at Hospital for Special Surgery located in New York City.

Dr. Zhao initiated the study while working in the laboratory led by Drs. Masamichi Takami and Ryutaro Kamijo at Showa University, Tokyo, where much of the work was performed. Dr. Zhao completed the study and extended the work to human cells during the past year at Hospital for Special Surgery working with Dr. Lionel Ivashkiv.

Specifically, the researchers discovered that downregulation of IRF-8 (meaning that the gene produces less IRF-8 protein) increases the production of cells called osteoclasts that are responsible for breaking down bone. An osteoblast is a type of cell that is responsible for forming

bone and an osteoclast is a type of cell that breaks down bony tissue (bone resorption). In humans and animals, bone formation and bone resorption are closely coupled processes involved in the normal remodeling of bone. Enhanced development of osteoclasts, however, can create canals and cavities that are hallmarks of diseases such as periodontitis, osteoporosis and rheumatoid arthritis.

Previous researchers have spent time identifying genes that are upregulated during enhanced development of osteoclasts, such as NFATc1, but few studies have identified genes that are downregulated in the process. To fill this knowledge gap, scientists at Hospital for Special Surgery, collaborating with researchers at other institutions, used microarray technology to conduct a genome-wide screen to identify genes that are downregulated during the formation of osteoclasts. They found that expression of IRF-8 was reduced by 75 percent in the initial phases of osteoclast development.

The researchers then genetically engineered mice to be deficient in IRF-8 and gave the animals x-rays and CT (computed tomography) scans to analyze IRF-8's influence on bone. They found that the mice had decreased bone mass and severe osteoporosis. Experiments demonstrated that this was due not to a decreased number of osteoblasts, but because of an increased number of osteoclasts. The researchers concluded that IRF-8 suppresses the production of osteoclasts.

Tests in human cells confirmed these findings. This included a study that showed that silencing IRF-8 messenger RNA in human osteoclast precursors with small interfering RNAs resulted in enhanced osteoclast production. In other words, decreased IRF-8 means more osteoclasts are produced.

This led the investigators to examine the effect of IRF-8 on the activity of a protein called NFATc1 that was previously reported to interact with

IRF-8. They found that IRF-8 inhibited the function and expression of NFATc1. This makes sense given that upregulation of NFATc1 is involved in triggering osteoclast precursor cells to turn into osteoclasts.

"This is the first paper to identify that IRF-8 is a novel key inhibitory factor in osteoclastogenesis [production of osteoclasts]," said Dr. Zhao. "We hope that the understanding of this gene can contribute to understanding the regulatory network of osteoclastogenesis and lead to new therapeutic approaches in the future."

Source: Hospital for Special Surgery