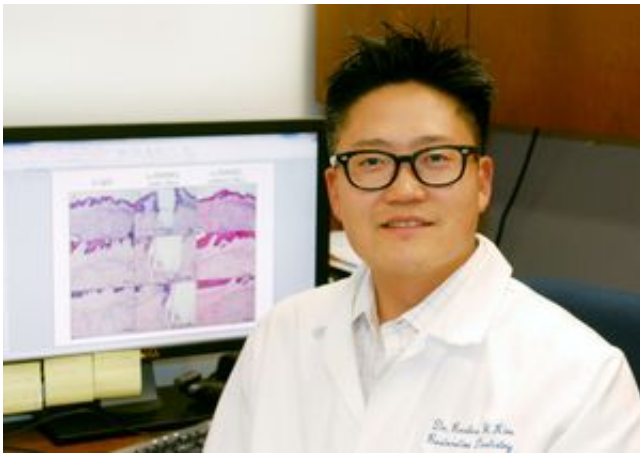


Study reveals new findings about cause of lesions around jaw bone

November 25 2014, by Brianna Aldrich



Osteonecrosis of the jaw is a debilitating and painful condition in which oral lesions develop in individuals taking drugs such as bisphosphonate or denosumab, which are commonly used in treatments for osteoporosis and for cancers that have spread to the bones. Although formally identified in 2003, the fundamental causes for osteonecrosis of the jaw (ONJ) development and its treatment remain unclear. New research provides a better understanding of how ONJ progresses and its cellular and structural activators, which could guide the development of therapeutic and preventive measures.

Diseases associated with [bone](#) loss such as osteoporosis are common in

older populations and in people who have bone-metastatic cancers. To prevent [bone loss](#) in vulnerable populations, patients take bisphosphonate, small molecules that bind tightly onto the bone, and denosumab, the neutralizing human anti-receptor activator of NF-kB ligand (RANKL) antibody. These drugs effectively inhibit the functions of [osteoclasts](#), which are the cells that break down bones.

However, for people taking these drugs, one of the most significant side effects is bisphosphonate-related or denosumab-related osteonecrosis of the jaw (BRONJ or DRONJ, respectively); this is defined as exposed dying bone and unclosed overlaying oral mucosa for at least eight weeks.

Scientists have speculated that these drugs cause ONJ based on how these drugs directly affect osteoclasts. However, the extent to which osteoclasts contribute to the development of ONJ remains uncertain. Researchers at the UCLA School of Dentistry have taken a new approach to understanding the development of ONJ.

A research team, led by Dr. Reuben Kim, associate professor of restorative dentistry and oral biology and medicine, developed and compared two different mouse models, one for BRONJ and one for DRONJ. In each model, Kim removed teeth to examine the physical characteristics that marked how ONJ progressed inside the mouse's mouth.

The BRONJ model was established by treating mice with bisphosphonate and the DRONJ model with mouse version of denosumab, anti-mouse-RANKL-neutralizing antibody that nullifies the functions of RANKL, which plays a critical role in determining how osteoclasts differentiate and form.

When the researchers compared the two mouse models, they found that lesions developed in 20 percent of the bisphosphonate models and in 50

percent of the denosumab models. Interestingly, lesions developed in the DRONJ model in the absence of osteoclasts because anti-mouse-RANKL antibody completely inhibited osteoclast formation.

This was an important finding because it suggests that the presence of osteoclasts may not be solely related to ONJ development. Rather, dysfunctional osteoclasts failed to break down all the bone at the wounded areas, and that may have caused the ONJ lesions. With this new revelation, the team surmised that it may be possible that progression of ONJ is primarily associated with structural defects, such as bone surfaces that failed to break down because of impaired functions or the formation of mature osteoclasts by bisphosphonates and denosumab, and not osteoclasts alone.

Taking this new finding one step further, the team examined the broken down bone structure around the ONJ lesion that formed where the tooth was removed in both mouse models. The comparison revealed a striking correlation between new bone formation within the sockets where teeth were extracted and complete wound closure.

The researchers said this suggested that newly formed bone or woven bone plays a key role during the healing process in the oral cavity. This led the team to posit that woven bone acts as a bridge between soft and hard tissues in the [oral cavity](#). Therefore, enhancing woven bone formation when osteoclasts fail to breakdown bone may help prevent ONJ development for patients who are taking [bisphosphonate](#) and denosumab.

More information: Drake W. Williams, Cindy Lee, Terresa Kim, Hideo Yagita, Hongkun Wu, Sil Park, Paul Yang, Honghu Liu, Songtao Shi, Ki-Hyuk Shin, Mo K. Kang, No-Hee Park, Reuben H. Kim, "Impaired Bone Resorption and Woven Bone Formation Are Associated with Development of Osteonecrosis of the Jaw-Like Lesions by

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