Researchers pinpoint how smoking causes osteoporosis

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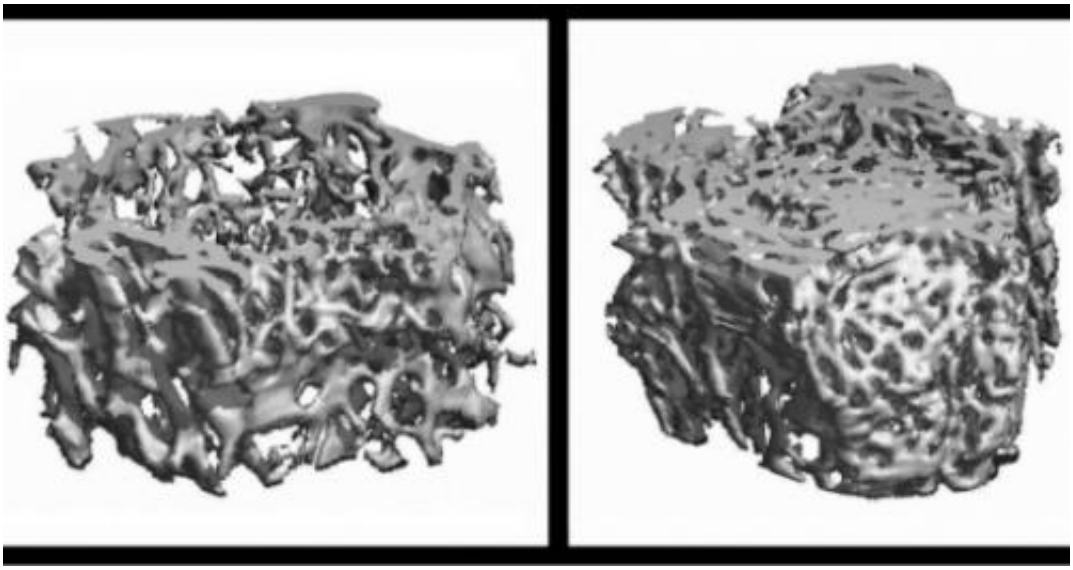

Mice whose AH-receptor genes were knocked out (rt) have much higher bone density than mice with the intact gene. Credit: JameeI Iqbal

(Medical Xpress)—Human bone breaks down and regenerates naturally all the time, in a perfectly balanced dance that maintains skeletal integrity.

As people age, bone tends to deteriorate faster, causing osteoporosis and other disorders. Smoking artificially accelerates bone degeneration as well.

For the first time, a joint team of researchers at the University of Pennsylvania and The Mount Sinai Medical Center have described the mechanics of how certain toxic compounds in smoke break down bone.

"It has been known from many epidemiological studies that smokers usually show bone loss, and their bone density is much lower than non-smokers' bone density," said Narayan Avadhani, Harriet Ellison Woodward Professor of Biochemistry and chair of the Department of Animal Biology in Penn's School of Veterinary Medicine. "What we show here is that excessive formation of osteoclasts by cigarette chemicals causes bone loss,"

Avadhani and Mone Zaidi, professor of medicine and of structural and chemical biology and director of the Mount Sinai Bone Program, co-authored "Smoke Carcinogens Cause Bone Loss Through the Aryl Hydrocarbon Receptor and Induction of Cyp Enzymes." They worked with Jameel Iqbal, former chief resident in pathology and laboratory medicine at the Hospital of the University of Pennsylvania, who completed his M.D. and Ph.D. at Mount Sinai in Zaidi's lab. The paper was published online in the *Proceedings of the National Academy of Sciences* of the United States of America.

In a natural process called bone remodeling, cells called osteoblasts build new bone while osteoclasts break down the bone matrix, releasing minerals and other molecules. RANK ligand, a regulatory protein molecule, determines the activity of osteoblasts and osteoclasts.

However, cigarette smokers suffer higher than normal skeletal degeneration rates and are more likely to get osteoporosis in the long run. Scientists have known this for a long time but did not understand how the mechanism behind smoking-related bone loss works.

When certain chemicals in cigarette smoke bind to the body's cellular

aryl hydrocarbon receptors, or AH-receptors, they stimulate excessive formation of osteoclasts, leading ultimately to bone loss in longtime smokers.

"Our study implicates a number of poly aryl hydrocarbons and dioxins found in tobacco smoke," Zaidi said, "and clarifies how those toxins enhance active bone breakdown to make the skeleton more fragile. It is our hope that these findings provide the conceptual framework for the design of novel therapies to help prevent and treat osteoporosis."

Collaborating with people at a number of institutions in the U.S. and abroad, scientists tested the smoke toxins benzo[a]pyrene, known as BaP, and tetrachlorodibenzo-p-dioxin, or TCDD, on mice.

They discovered that the AH-receptor works through the activation of a group of cytochrome P450 enzymes known as Cyp1. When the genes that turn on the function of Cyp1 enzymes was knocked out, their AH-receptors failed to induce osteoclast formation and hence bone loss, effectively cutting off the source of bone degeneration. Cyp1 genes are therefore crucial for cigarette smoke induced bone loss.

In the course of their research, the scientists were surprised to find that RANK ligand was the key to inducing the progenitor cells that make osteoclasts, and that this ligand is also regulated by the AH receptor, Avadhani said.

The study has implications for drug therapies that could potentially target the AH receptor with a specially designed molecule. Eventually, a therapeutic approach could be taken to help prevent osteoporosis in smokers and non-smokers, the researchers said. Because activation of the AH receptor also affects other parts of the body besides the skeleton, the trick is to find a solution that is specific to bone.

"Currently, we have a grant proposal ready to go to study how to prevent bone loss," Avadhani said.

For now, this study, funded by a National Institutes of Health collaborative research grant between the two groups, has expanded the current understanding of why smokers are more prone to bone degradation, said Iqbal, who is now in clinical pathology in the VA Greater Los Angeles Healthcare System.

More information: www.pnas.org/content/early/201 … /1220919110.abstract

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