The Plot Thickens on Thin Bones

The signals that keep bones strong deteriorate with age. New findings reveal why, and researchers are using the knowledge to develop ways to treat osteoporosis

R. John Davenport

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With age, bones thin and weaken, leaving the elderly susceptible to fractures. The affliction, known as osteoporosis, strikes millions of people, especially postmenopausal women. Recent strides in understanding the signals that control whether bone grows or shrinks offer insight into the causes of osteoporosis and promise to lead investigators to a new class of treatments. In addition, research is illuminating links between bone loss and other health problems such as heart disease.

It’s a common image of age-related frailty: a shrunken elderly woman bent over a cane, walking gingerly down the street for fear of falling. Although no one dies directly from osteoporosis, debilitating and sometimes deadly fractures can result. According to the U.S. National Institutes of Health, the disease afflicts 8 million women and 2 million men in the United States, with another 34 million at risk because of low bone density; most of these people are over age 50. Treating osteoporosis and associated fractures costs billions of dollars each year.

Age isn’t the only risk factor for osteoporosis. A diet low in calcium or vitamin D, smoking, and long-term treatment with glucocorticoids (used for arthritis and asthma) also ramp up the probability. Calcium supplements and exercise help bone stay strong and prevent the disease; furthermore, treatments to stop bone loss are available. In postmenopausal women, hormone replacement therapy (HRT) slows bone loss spurred by a drop in estrogen concentrations, although patients and health care providers must weigh the benefits of the therapy against apparent increased risks of cancer and heart disease (see Web Links: “Sorting Through the Confusion Over Estrogen” and “The Search for Alternatives to Hormone Replacement Therapy”). In addition, calcitonin, a naturally occurring hormone, reduces bone loss in postmenopausal women, and some data suggest that testosterone replacement protects bone in men with extremely low testosterone concentrations. Nonhormonal alternatives also exist. Compounds called bisphosphonates—derivatives of pyrophosphate, a chemical that regulates calcium storage and release in the body—also retard bone thinning.

These existing therapies “put out the fire” of bone loss, says bone biologist Steven Teitelbaum of Washington University in St. Louis, Missouri. But they fail to rebuild what’s burned away: They squelch cells called osteoclasts that chew up bone, but they don’t urge the body to make new bone. “We’re pretty good at preventing the disease,” he says. “The issue is going to be, can we increase bone mass [once it declines]?” As researchers illuminate the competing forces that build up and break down the skeleton, however, they are getting leads on new ways to spur bone growth, with the first such treatments already in view. The discoveries aren’t just shedding light on how to curb osteoporosis; they are revealing links between bone loss and other diseases of aging, including heart disease.

A Delicate Balance

Without a skeleton, soft tissue would collapse and muscles would have nothing to pull against. But bones aren’t static trusses, like I-beams in a skyscraper: They teem with living cells. Throughout a person’s life, bones undergo renovation. Osteoclasts constantly chew up bone. They do so by spewing acid into a tightly sealed space between themselves and the bone; the pH drop dissolves the calcium and phosphate crystals that coat bone. Enzymes secreted by osteoclasts digest bone’s protein scaffold. After the excavation process is complete, bone-building cells called osteoblasts step in. These cells discharge fresh collagen, which link to form the scaffold. Osteoblasts also regulate mineralization of this collagen matrix with calcium and phosphate, although how they do it is not well understood.

Like any efficient construction job, bone remodeling requires the coordination of the specialized teams. If osteoclasts outwork osteoblasts, bone—especially the meshlike trabecular type that fills vertebrae and the ends of long bones—thins and osteoporosis results (see “Teaching Resources: Osteoporosis Images”). At the opposite extreme, genetic defects that cripple osteoclasts cause bone to thicken, a condition called osteopetrosis. The overgrowth of bone crowds out nerves, blood vessels, and bone marrow, leaving affected individuals in pain and at risk for stroke and infection.

Organisms carefully regulate osteoclast and osteoblast function to keep the opposing forces in balance. Osteoclasts arise from macrophages, whereas osteoblasts start their lives as mesenchymal stem cells, precursors to connective tissue cells. The signals that spur osteoclast formation are better understood than those that nurture osteoblasts. Proteins named RANKL and M-CSF bind to cell surface receptors on macrophages and trigger signaling pathways that cause the cells to proliferate and transform into osteoclasts. Osteoblasts and their precursors make RANKL and M-CSF in response to vitamin D and parathyroid hormone, an example of how the body coordinates bone-building and -breaking activities. Recent studies are adding other molecules to the picture (see “SHIPping Out
Bone Breakers”§ and “RAINing on the RANK Parade” ll). The findings suggest potential new drug targets, but therapies that stop osteoclasts would, like current drugs, slow bone loss rather than promote growth of new bone.

To zero in on bone-building drugs, scientists are unveiling what makes osteoblasts tick. Although an understanding of osteoblast biology has lagged behind that of osteoclast biology, recent discoveries are solving some of the mysteries. In 1997, three research teams identified the first regulator of osteoblast formation, a protein called Cbfa1. Defects in the protein impair embryonic skeletal development; mounting evidence suggests that Cbfa1 promotes bone remodeling in adult animals, and scientists are pinpointing other molecules that are involved.

Studies of rare bone diseases have uncovered the newest player. In November 2001, Yaoqin Gong of Case Western Reserve University in Cleveland, Ohio, and colleagues identified the genetic alteration responsible for osteoporosis-pseudoglioma syndrome (OPS; also known as OPPG), a rare disease that afflicts children (see “Skeleton Crew”¶). Affected individuals suffer from frequent fractures because of low bone density. Genetic analysis revealed that patients carry a mutation in the lrp5 gene; this gene produces a protein component of the Wnt signaling pathway, which governs bone patterning during embryonic development. The study was the first to suggest that Wnt might also influence bone remodeling. Cell-culture experiments by the team suggested that the mutation blocks the Wnt signal and prevents osteoblasts from maturing. Then, early this year, two groups independently pinpointed a second mutation in lrp5 that is passed down in families with abnormally high bone mass: Instead of crippling lrp5, the change apparently cranks up the Lrp5 protein’s activity, encouraging extra bone growth.

Studies of mice have supported the putative effects of the two mutations. Mice that carry the mutation linked to human OPS display many of the disease’s signs, including a reduced number of osteoblasts, low bone density, fractures, and abnormally high numbers of blood vessels in the eye, reported Masaki Kato of Baylor College of Medicine in Houston, Texas, and colleagues in the April 2002 Journal of Cell Biology. And the high-bone-mass mutation in human lrp5 also makes bone more dense when introduced into mice, according to a presentation by Frederick Bex of Wyeth in Collegeville, Pennsylvania, and colleagues at the annual meeting of the American Society for Bone and Mineral Research in September. Osteoblasts in these animals are more active, apparently because the cells die more slowly than in normal animals.

As researchers investigate ways to activate the Wnt pathway and encourage bone growth, one bone-growing treatment—parathyroid hormone (PTH)—is ready to hit the market. As its name suggests, PTH is a hormone churned out by the parathyroid gland; the molecule regulates the amount of calcium circulating throughout the body by controlling uptake in the intestine and resorption from bone. PTH doesn’t act directly on osteoclasts; instead, it prods osteoblasts to manufacture RANKL, which stimulates osteoclast formation. PTH normally increases resorption of bone, but if given in daily bursts, the hormone instead cranks up bone formation—probably by extending the life of osteoblasts—and increases bone density. The U.S. Food and Drug Administration approved the pharmaceutical company Eli Lilly’s formulation of PTH in July for this use.

New Twists on Old Favorites

As some scientists probe emerging molecular pathways for new drug targets, others are harnessing molecules long known to be important in bone health and directing them in novel ways. Vitamin D is crucial for a healthy skeleton because it ensures that calcium and phosphorus are readily available in the blood, from which the minerals can be deposited into new bone. Genetic analysis revealed that patients carry a mutation in the lrp5 gene; this gene produces a protein component of the Wnt signaling pathway, which governs body patterning during embryonic development. The study was the first to suggest that...
Lawrence Riggs of the Mayo Clinic in Rochester, Minnesota.

...drugs could potentially be important,” says endocrinologist mounting controversy surrounding HRT, “this new class of mor growth in the animals’ reproductive tissue. In light of the terone. Moreover, unlike HRT, the compound did not spur tu-

GELS, for activator of nongenotropic estrogen-like signals—

ports the identification of compounds—which they call AN-

work published in the 25 October issue of Science.

be that hormone. Two years ago, his team showed that obese mice with defects in leptin signaling have abnormally high bone mass. Leptin appears to be acting through the hypo-

muses in the brain rather than directly on bone cells: The hor-

none did not alter osteoblast signaling in cell culture, but when infused into the brains of leptin-deficient mice, it brought bone mass back to normal. The possibility that the brain regulates bone balance through leptin was tantalizing, but how the nervous system and bone connect remained mys-

terious (see “No Bones About It**”).

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Taking Bone to Heart

The fact that leptin centrally controls both body weight and bone density highlights the fact that disparate biological processes are connected. Work during the last few years has elucidated molecular ties between the skeleton and the cardiovascular system. In addition to accumulating fatty, cholesterol-filled plaques, arteries can amass calcium deposits that stiffen the vessels and force the heart to work harder. These deposits aren’t amorphous blobs; they are structured like bone. Research over the last decade has revealed that the deposits accumulate because immature smooth muscle cells turn into osteoblast-like cells that produce bone-building proteins. Ironically, osteoporosis and calcification of arteries frequently go hand in hand, says rheumatologist Linda Demer of the University of California, Los Angeles, who has shown that oxidative damage (see “The Two Faces of Oxygen”††) plays a crucial role in the process. Her team reported last year in *Free Radical Biology and Medicine* that oxidized lipids, which amass in atherosclerosis and cause inflammation, have opposite effects on vascular and bone cells in culture: Oxidized lipids prompted vascular cells to specialize into bonemakers, whereas the same molecules killed osteoblast precursor cells. Agents that simulate production of reactive oxygen species also deliver a death blow to the same cells, indicating that the effect arises from generalized oxidative damage. And in a study published in April in the *Journal of Biological Chemistry*, the team showed that hydrogen peroxide and oxidized lipids spur the maturation of bone-degrading osteoclasts in the skeleton. Together the results suggest that oxidatively damaged molecules spur bone loss in the skeleton and accumulation of bonelike deposits in blood vessels.

Demer postulates that the discrepancy stems from evolution’s antidote to invading microbes. Degrading bone after a bacterial attack would remove the matrix on which the bugs grow. If microorganisms invade a blood vessel, on the other hand, “you wouldn’t want to try to dissolve the artery wall,” says Demer. Instead, she says, building a bone casing would wall off the invaders and prevent them from spreading. But these strategies can backfire in both the heart and the skeleton. In heart disease, which is caused by chronic inflammation, excess calcification weakens arteries and increases the likelihood that lipid plaques will break off and block a blood vessel. Osteoporosis might also arise in part from inflammation, Demer speculates. Her group has found that the skeleton contains lipids; if damaged, these lipids could fire up osteoclasts and kill osteoblasts, resulting in thin bones.

In response to inflammation and elevated lipid quantities, “there seems to be a reciprocal relationship between mineral metabolism in the skeleton and [in] the vasculature,” says molecular biologist Dwight Towler of Washington University: Under conditions where bone disintegrates, calcium builds up in blood vessels. His team is investigating the function of a population of cells in vascular tissue with the stem cell–like capacity to turn into osteoblasts, as well as the molecular signals that trigger such a transition. The work could point toward new treatments for both heart disease and osteoporosis. Hints that such a quest could be fruitful already exist. Statins—widely prescribed to reduce cholesterol and possibly effective in preventing or treating Alzheimer’s disease (see *Helmuth Science* article†‡)—reverse bone loss when administered to rodents; human studies of statin haven’t produced a clear picture of the drugs’ effect on bone. Formulations for humans are designed to target the liver, not bone, but new variations could deliver a stiffer punch to osteoporosis. As scientists further flesh out the signaling pathways that spur bone formation and bone degradation, they’ll likely deduce how bone remodeling is integrated into the body’s overall physiology. This information should illuminate reasons why bone—and other tissues—degrade with time.

Osteoporosis might not kill like aging-related diseases such as cancer and heart disease do, nor does it inflict the same psychological stress on families as Alzheimer’s disease does, but the common malady restricts the mobility of older people and reduces their quality of life. Researchers hope that the current progress in understanding bone biology will reveal new ways to manipulate it. Resulting treatments might not just plug the skeleton’s holes but also fill them back up.

R. John Davenport is an associate editor of SAGE KE. He hasn’t put his osteoblasts to a real test since a skateboarding accident in sixth grade.

Further Reading


†† sageke.sciencemag.org/cgi/content/full/sageke;2002/34/or9

‡‡ sageke.sciencemag.org/cgi/content/abstract/sageke;2002/44/ns8