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Speeding up bone growth by manipulating stem cells

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Qian Wang at work among plants that host some of the building blocks of his nanomolecular scaffolds.

If you break a bone, you know you'll end up in a cast for weeks. But what if the time it took to heal a break could be cut in half? Or cut to just a tenth of the time it takes now? Qian Wang, a chemistry professor at the University of South Carolina, has made tantalizing progress toward that goal.

Wang, Andrew Lee and co-workers just reported in *Molecular Pharmaceutics* that surfaces coated with bionanoparticles could greatly accelerate the early phases of bone growth. Their coatings, based in part on genetically modified Tobacco mosaic virus, reduced the amount of time it took to convert stem cells into bone nodules – from two weeks to just two days.

The key to hastening bone healing or growth is to coax a perfectly natural process to pick up the pace.

"If you break a rib, or a finger, the healing is automatic," said Wang. "You need to get the bones aligned to be sure it works as well as possible, but then nature takes over."

Healing is indeed very natural. The human body continuously generates and circulates cells that are undifferentiated; that is, they can be converted into the components of a range of tissues, such as skin or muscle or bone, depending on what the body needs.

The conversion of these cells – called stem cells – is set into motion by external cues. In bone healing, the body senses the break at the cellular level and begins converting stem cells into new bone cells at the location of the break, bonding the fracture back into a single unit. The process is very slow, which is helpful in allowing a fracture to be properly set, but after that point the wait is at least an inconvenience, and in some cases highly detrimental.

"With a broken femur, a leg, you can be really incapacitated for a long time," said Wang. "In cases like that, they sometimes inject a protein-based drug, BMP-2, which is very effective in speeding up the healing process. Unfortunately, it's very expensive and can also have some side effects."

In a search for alternatives four years ago, Wang and colleagues uncovered some unexpected accelerants of bone growth: plant viruses. They originally meant for these viruses, which are harmless to humans, to work as controls. They coated glass surfaces with uniform coverings of the Turnip yellow mosaic virus and Tobacco mosaic virus, originally intending to use them as starting points for examining other potential variations.

But they were surprised to find that the coatings alone could reduce the amount of time to grow bone nodules from stem cells. Since then, Wang and co-workers have refined their approach to better define just what it is that accelerates bone growth.

Over the course of the past four years, they've demonstrated that it's a combination of the chemistry as well as the topography of the surface that determines how long it takes a stem cell to form bone nodules. The stem cells are nestled into a nanotopgraphy defined by the plant virus, and within that nanotopography the cells make contact with the variety of chemical groups on the viral surface.

Wang and his team are now asserting control over these variables. In the most recent effort spearheaded by Lee, they built up a layer-by-layer assembly underneath the virus coating to ensure stability. They also genetically modified the viral protein to enhance the interaction between the coating and the stem cells and help drive them toward bone growth.

Their efforts were rewarded with bone nodules that formed just two days after the addition of stem cells, compared to two weeks with a standard glass surface. They're also carefully following the cellular signs involved with success. BMP-2 is involved, but as an intrinsic cellular product rather than an added drug.

"BMP-2 is bone morphogenetic protein 2. It can be added as a protein-based drug, but it's a natural protein produced in the cell," said Wang. "We see upregulation of the BMP-2 within 8 hours with the new scaffold." They also find osteocalcin expression and calcium sequestration, two processes associated with bone formation, to be much more pronounced with their new coatings.

"What we've seen could prove very useful, particularly when it comes to external implants in bones," said Wang. "With those, you have to add a foreign material, and knowing that a coating might increase the bone growth process is clearly beneficial."

"But more importantly, we feel we're making progress in a more general sense in bone engineering. We're really showing the direct correlation between nanotopography and cellular response. If our results can be further developed, in the future you could use titanium to replace the bone, and you might be able to use different kinds of nanoscale patterning on the titanium surface to create all kinds of different cellular responses."

Chuanbin Mao, a professor in the department of chemistry and biochemistry at the University of Oklahoma who was not involved in the work, wrote in an e-mail that he was "amazed and excited" by the results. "The display of peptides on viruses, including Tobacco mosaic virus, is a powerful approach for studying how engineered virus particles can direct stem cell differentiation."

"The discovery that the display of a cell adhesion peptide on Tobacco mosaic virus can enable the rapid differentiation of stem cells into bone-forming cells is very important for guiding scientists in designing a scaffold that can induce rapid bone formation in regenerative medicine."

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