Medical Xpress

# Timing is everything when using oxygen to regenerate bone

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A research team at Tulane University will report this week that the application of high levels of oxygen to a severed bone facilitates bone regrowth, study results that may one day hold promise for injured soldiers, diabetics and other accident victims.

The results of the Department of Defense-funded study will be presented on Monday April 23, at the American Society for Biochemistry and Molecular Biology annual meeting, held in conjunction with the Experimental Biology conference in San Diego.

"One out of every 200 Americans is an amputee," emphasizes Mimi Sammarco, who led the study at Tulane. "This number is expected to double in the next 40 years and is of particular concern given that amputation injuries have increased considerably due to combat casualties and the increasing amputation issues associated with the rise in diabetes and other related diseases."

The only vertebrate capable of regenerating lost limbs is the salamander, which has been the focus of a number of studies by the laboratory where the work was done. Run by Ken Muneoka, a professor at Tulane's cell and molecular biology department, the lab has been exploring the molecular underpinnings of limb regeneration under various circumstances. The work spearheaded by Sammarco, meanwhile, uses a mouse model.

"While salamanders are able to regenerate entire limbs, rodents, monkeys and humans are only able to regenerate the digit tip after amputation," she explains. "The third phalangeal element, the very end bone on your finger, if you amputate one-third back or anywhere toward the tip, it will grow back. If you go just a fraction of a millimeter closer, it won't. If you amputate in the middle bone, it won't."

Multiple research teams have been trying to figure out what makes that huge difference between regrowth here but no regrowth there. The Tulane lab, in particular, has been investigating which genes are turned on, which proteins are expressed and which molecular activities change at the site of amputation over time.

"What it boils down to is genes (that spur regeneration) don't just turn themselves on. They turn on because something signals them. So I thought, maybe it's oxygen that's turning them on," Sammarco says. "Oxygen is often the primary signal that turns on various genes."

Sammarco used a special incubator to expose a thin bone sample taken from an amputation site to high levels of oxygen. "What we found is that when you expose regenerating bone to 20 percent oxygen, it'll respond very favorably but only at a certain time. If you try it too early, like right after amputation, it doesn't do a whole lot."

The air we breathe is made of about 20 percent oxygen, but that's a lot higher than the level in the body, which is closer to around 6 percent, she explains. "In some areas of injury, the oxygen level is going to go down to 1 percent," because the blood vessels that deliver oxygen to tissue naturally retract after injury. "And maybe we're only talking millimeters or fractions of millimeters. They're naturally contractile."

What to do about the drop in oxygen levels is something of a puzzle for those in the wound-healing field, Sammarco says. Many researchers are trying to figure out how to reinvigorate vasculature and how to oxygenate the wound site.

"There are two opposing fields: We get injured, so we need to drop the oxygen concentration to encourage vasculature. And then there's the other side that says, no, we need to flood it with oxygen to oxygenate the tissue. And neither works particularly well," she admits.

The way Sammarco sees it, maybe it's not an either-or situation: "I think you have to know when to apply each one. It's all about timing. Obviously, there's a sequence in growing things back. And oxygen can push the button that has to be applied at a certain time."

Ultimately, battlefield doctors must be able to assess in what stage a patient is in the spectrum of injury and repair.

"Further on down the line, how do we make that treatable in the field in the middle of the desert? How do you make it portable and usable? There's general public usable and there's where it is going to be most useful, and that's in the field -- immediate treatment for a soldier so we can have maximal bone growth down the line."

Sammarco emphasizes that even just partial regeneration of a limb would make a world of difference to any amputee and that soldiers in particular are excellent candidates for rehabilitation, because they are usually in fantastic physical shape.

"They're the fittest people out there. They're not diabetics receiving amputations. They're not the average American who received an amputation after a car crash. These are the most viable people for rehabilitation, and these are the people who can benefit from getting an extra inch of stump length and be able to ski – to do things they were doing before, because their level of activity is so much higher than everybody else's," she says. "Thus, every effort to direct and control the extension of amputation stump length contributes to the rehabilitation of amputees, while keeping in mind the long-term goal of complete regeneration."

Provided by American Society for Biochemistry and Molecular Biology