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Feature: Biomedicine,Health,Cells

Cells from fat mend bone, cartilage, muscle and even the heart

Adipose tissue is a natural storehouse of healing cells

By Susan Gaidos 2:30pm, March 9, 2016

FAT AS A FIXER Adipose tissue, a collection of fat-storing cells (red) surrounded by connective tissue (yellow), has its own supply of blood and immune cells.

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Most people would be happy to get rid of excess body fat. Even better: Trade the spare tire for something useful — say, better-functioning knees or hips, or a fix for an ailing heart or a broken bone.

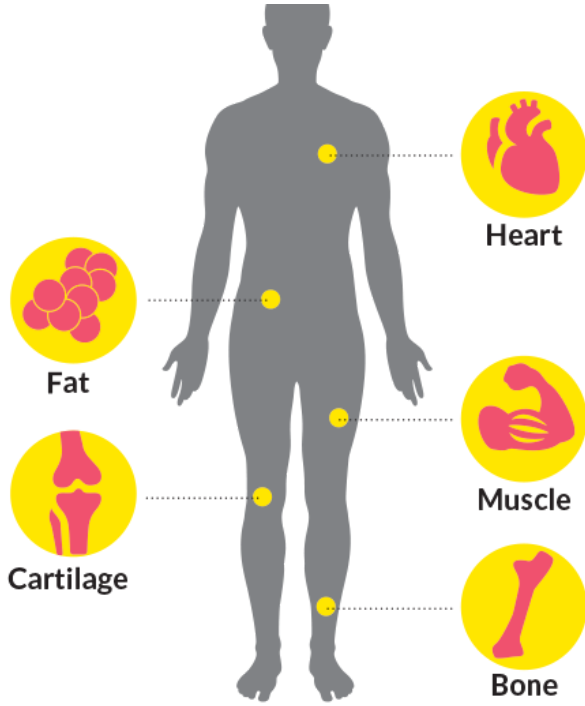
The idea is not far-fetched, some scientists say. Researchers worldwide are repurposing discarded fat to repair body parts damaged by injury, disease or age. Recent studies in lab animals and humans show that the much-maligned material can be a source of cells useful for treating a wide range of ills.

At the University of Pittsburgh, bioengineer Rocky Tuan and colleagues extract buckets full of yellow fat from volunteers' bellies and thighs and turn the liposuctioned material into tissue that resembles shock-absorbing cartilage. If the cartilage works as well in people as it has in animals, Tuan's approach might someday offer a kind of self-repair for osteoarthritis, the painful degeneration of cartilage in the joints. He's also using fat cells to grow replacement parts for the tendons and ligaments that support the joints.

Foremost among fat's virtues is its richness of stem cells, which have the ability to divide and grow into a wide variety of tissue types. Fat stem cells — also known as adipose-derived stem cells — can be coerced to grow into bone, cartilage, muscle tissue or, of course, more fat.

Multipurposes

Cells from fat are being tested to mend tissues found in damaged joints, hearts and muscle, and to regrow bone and heal wounds.



M. Telfer

Sources: D.M. Minteer et al/Clin. Plastic Surg. *2015; A.J. Leblanc* et al/Stem Cells Transl. Med. *2013*

The stem cells in fat share the medical-worthy spotlight with a few other cells. Along with the fat-filled adipocytes that store energy, fat tissue has its own blood supply and supporting connective tissue, called stroma. The stroma contains blood cells, immune cells, endothelial cells that line the inner surface of blood vessels and pericytes, which line the outer surface. These other fat-derived cells are proving to have therapeutic value as well.

Plastic surgeon J. Peter Rubin, also at Pitt, says that the multitalented cells found in fat could prove to be the ultimate body repair kit, providing replacement tissue or inspiring repair of body parts that can't mend themselves.

Much of the research — more than a decade of studies — has been in lab animals, but a few applications are being tested in human volunteers. Current clinical studies under way aim to provide replacement tissue to treat chronic wounds and diabetic sores, or conditions such as Parkinson's disease, multiple sclerosis, chronic obstructive pulmonary disease and type 1 diabetes.

Most clinical studies use the simplest approach: Harvest cells from a patient, then inject them in a single procedure. In more complex approaches still in lab and animal testing, various cells in fat are extracted and manipulated to create custom treatments for worn-out or damaged tissues or to generate blood flow after a heart attack or replace bone in large fractures.

Questions remain, however, about how the cells do their regenerative magic. Scientists and regulators still have plenty to figure out, such as what cell characteristics work best for each application.

A lush source

Stem cells can develop into various cell types, which makes them the focus of studies that aim to replace cells that fail because of disease, accident or age. Stem cells taken from embryos are more versatile than other types of stem cells, but their use is controversial. For that reason, researchers have studied stem cells from sources other than embryos, including bone marrow, muscle and blood.

Fat tissue comes from the same embryonic tissue as bone marrow, a traditional stem cell source, so scientists reasoned that fat might contain similar cells. In 2002, UCLA researchers discovered stem cells in human fat. They were surprised to find vast quantities.

Stem cells make up 2 to 10 percent of fat tissue. A cubic centimeter of liposuctioned fat (about one-fifth of a teaspoon) yields 100 times as many stem cells as does the same amount of bone marrow, Tuan says. And fat cells are easy to harvest — much easier than bone marrow. One pound of fat removed from a patient's abdomen can yield up to 200 million stem cells, a more than adequate supply for treatments.

Why fat produces so many stem cells isn't clear, but Rubin points out that fat tissue serves several important

Why fat produces so many stem cells isn't clear, but Rubin points out that fat tissue serves several important functions. In addition to storing and releasing energy, it helps insulate and protect the body's internal organs. "Like most tissues in the body, fat has a reservoir of stem cells to replenish cells as they die off or create new cells in response to growth or the need for more cells," he says.

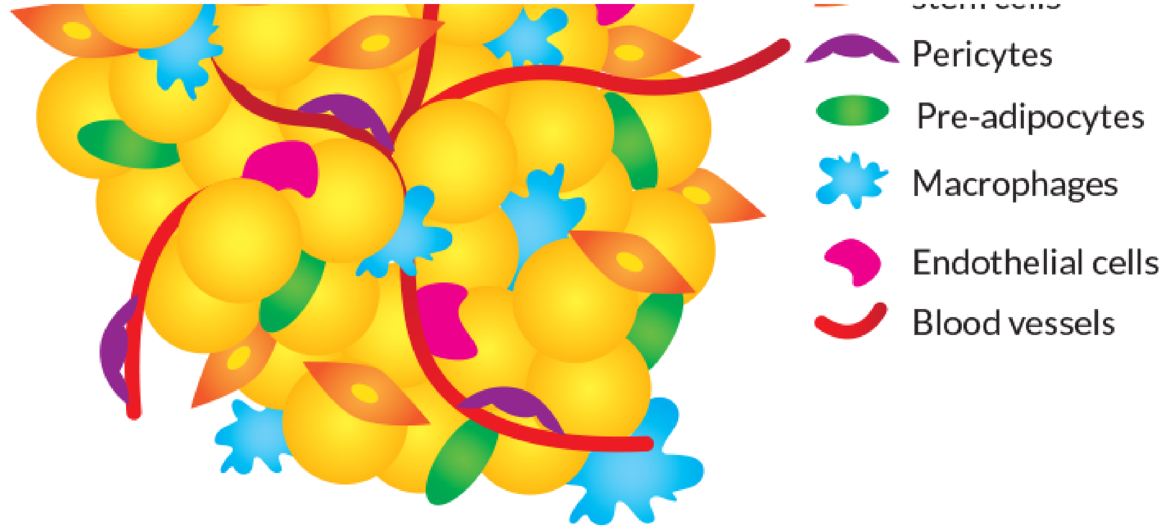
Fat produces so many stem cells, in fact, that for some applications — such as tissue-replacement or "fat grafting" — there's no need to grow more of them in the lab. Once harvested, liposuctioned material is treated with enzymes to remove cells from the surrounding tissue, then put into a centrifuge to separate the stem cells from other cell types. In about an hour, the stem cells are ready to be injected back into the patient to plump skin or round out fat tissue lost to injury or disease. Rubin has used this method to treat patients who have lost tissue during breast cancer surgery or have been injured in war. His lab is conducting a clinical trial on the use of fat stem cells to plump up tissue at the site of an amputation to improve the comfort and fit of a prosthetic arm or leg or to make it easier to tolerate sitting for long periods in a wheelchair.

Already, Rubin's team has treated five military patients, extracting fat from each patient's abdomen and injecting the stem cells back into the patient at the injury site. He and other scientists think that the fat stem cells remodel tissue by releasing growth factors and communicating with surrounding cells in their new location — sending and receiving signals through chemical cues. As a result, the stem cells enhance the growth of new fat tissue and boost blood supply to surrounding tissue. Over a period of several weeks, the cells he injects form a mound of fat tissue, allowing patients to fit a prosthesis or sit without pain. So far, all of the patients have benefited from the stem cell injections, he says, though his group is still working on how much to inject for each patient.

Story continues after graphic

What's in fat?

Fat is an organ with a complex assembly of cells. In addition to fat cells, or adipocytes, and blood vessels, fat tissue contains stem cells, pericytes (cells that stabilize blood vessel walls), pre-adipocytes (precursors to fat cells), macrophages (immune cells) and endothelial cells, which form the inner lining of blood vessels.



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Stretching limits

Other applications require manipulating cells in the lab, placing fat stem cells in a specific environment — and sometimes putting mechanical pressure on them — to direct the cells to transform into certain cell types.

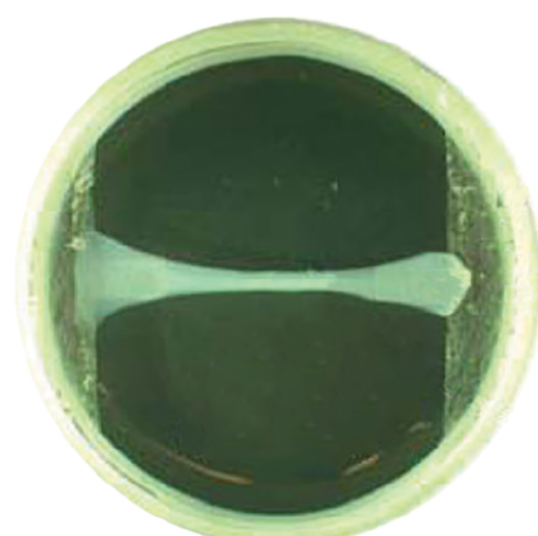
Tuan's group at Pitt places fat stem cells on scaffolds that help guide the growth of the cells, developing treatments to regenerate anterior cruciate ligament tissue or to repair rotator cuff injuries and Achilles tendon ruptures. Injury to ligaments and tendons is common, especially among athletes, but tears or worn-down areas generally don't heal completely by themselves. Efforts to create substitute tissues have largely failed, Tuan says, because re-creating the structure of a tendon or ligament remains a challenge.

Tendons are the cables that connect muscle to bone, allowing arms to rotate at the shoulder, knees to bend or fists to clench. Cells in tendons, called tenocytes, line up along long fibers of collagen, creating molecular bridges that reach across and intertwine with collagen cables to help give them strength and flexibility. This structure allows tendons to be stretched up to 15 or 20 percent beyond their original length and snap back into shape.

Tuan's group has discovered a trick for turning fat stem cells into tenocytes that grow in the same organized way. In 2013, the researchers outlined the method in *Biomaterials*. To replicate the structure of natural tissues, the scientists created scaffolds of biodegradable nano-sized fibers. Fat cells were then combined with bovine collagen and placed, or seeded, into the scaffold. The tiny fibers interacted with the stem cells, sending and receiving instructions that guided the stem cells' growth. Over seven days, as the stem cells differentiated into tenocytes, the scientists applied mechanical force on the ends of the scaffold — pulling the structure to keep the cells under tension just like a natural tendon would do during motion.

By tugging on fat stem cells, Tuan says, the group can create replacement tendons that are strong, stiff and resilient, like natural human tendons.

Tuan's group is also exploring 3-D printing to create artificial cartilage from fat stem cells.



Applying tension to reprogrammed human fat stem cells yields stretchable tendons that can bear weight.

Printing parts

Cartilage is a flexible tissue that serves as padding between bones, allowing knees, fingers, hips and shoulders to move freely. When cartilage wears down, the result is osteoarthritis, a painful condition that affects one in four people, often those over age 65.

Once cartilage is damaged, it continues to deteriorate, forming what Tuan calls "potholes." Over time, the potholes grow, eventually reaching the bone. The standard solution is a joint replacement. In the United States, more than 1 million people get knee or hip replacements each year.

G. Yang et al/Biomaterials 2013

Tuan calls the process “rebuilding the road.” The invasive procedure requires surgically replacing the joint with plastic and metal parts that generally last 10 to 15 years. Because an increasing number of people get new joints in their 40s or 50s, many require more than one round of surgery. “But there’s a limit to the number of times you can do that,” he says.

Tuan’s 3-D printing method builds thin layers of fat stem cells into a custom-sized scaffold to create new cartilage in the size and shape needed. The “ink” is made of fat stem cells plus gelatin, which consists of proteins found in living tissue. The scientists chemically modify the gelatin so that the ink remains fluid during printing. Once printed, the material is irradiated with light so that enzymes in the mixture form bonds, cross-linking to create stiffer, cartilage-like material.

The procedure has been used to create cartilage implants for rabbits and goats. Animals that once hobbled were able to hop, trot and otherwise move about, according to a report last August in *Frontiers in Bioengineering and Biotechnology*.

“Because the engineered cartilage is a living tissue … unlike a metal or polymer implant, it is expected to continue to grow into its natural shape and function once it is implanted into the joint,” Tuan says. “No replacement is therefore necessary.”

Still, it’s not the ideal solution, Tuan admits. “The problem is that’s not how tissues are formed,” he says. “Tissues form when cells migrate to a place, make themselves at home and build their own support structure, or matrix.”

His group is now devising ways to allow fat stem cells to set up their home right at the site of the pothole. The vision is to create a minimally invasive procedure, giving doctors a tool they can thread through a catheter to print the fat-derived stem cell cartilage at the site of the damage, inside the joint. Fat stem cells could then settle in and multiply directly in the joint. Additional arthroscopic instruments, also under development in Tuan’s lab, will allow physicians to guide the injection and smooth out newly printed cartilage to create a perfect fit that closely resembles the real thing.

So far, each step in the new approach has been developed. The next step is to tie all the pieces together in animal studies.

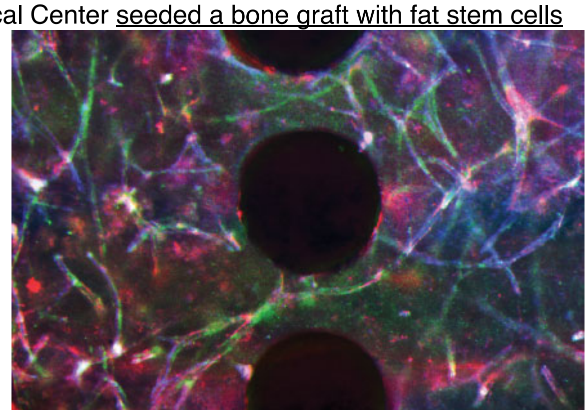
Boning up on body repair

The body does a better job of healing broken bone than healing cartilage. But if the fracture is large or a significant amount of bone is lost, the bone may not heal. In such cases, surgeons can take bone from another part of the patient’s body, or use bone from a cadaver, to fill in the gap. Biomedical engineer Warren Grayson of Johns Hopkins University says more than 1 million bone replacement procedures are performed each year in the United States, often after accidents or tumor removal. The surgery is invasive and carries risks of rejection, infection and lingering pain.

A better option, Grayson says, is to help patients grow bone from their own fat cells. Because the bone-growing material comes from the patient’s body, the grafts are less likely to get rejected than cells from donor tissue. What’s more, the bone may later grow with the patient, potentially eliminating the need for multiple surgeries in children who receive grafts but still have growing to do.

Since 2010, Grayson’s team has been growing bone from liposuctioned fat and successfully implanting the bone in animals. Stem cells taken from fat are placed in a bioreactor, an incubator--like device that nourishes cells as they grow on a scaffold for five weeks. Added nutrients and growth factors help the cells transform into bone cells.

Already, fat stem cells have been used in a few trials to help regenerate bone in people. In 2004, German doctors successfully used stem cells collected from a 7-year-old’s fat, along with other cells, to repair damage to her skull. Five years later, scientists at Cincinnati Children’s Hospital Medical Center seeded a bone graft with fat stem cells to replace a teen’s missing facial bones.



In the case of the teen, fat stem cells were injected onto a scaffold from donor bone. But such bone grafts require multiple surgeries and don’t come with a ready blood supply to nourish the new bone as it grows.

Grayson’s group aims to make the repair process easier on the patient. He and his team are growing fully functioning bone — with its own blood supply — from fat. Each graft can be custom-designed, using 3-D modeling and printing, to fit precisely where needed.

His team is experimenting with different formulas — and two different cell types from fat — to find the best ways to form all the cell types needed.

More recently, his group tested fat-derived stem cells against bone marrow cells in creating new bone. The fat stem cells outperformed the bone marrow stem cells. The findings, published in the September 2015 *Stem Cells*, show that in the presence of specific growth factors over a period of weeks, fat stem cells produced more calcium and bone mineral deposits per cell than did the bone marrow stem cells.

After 14 days in a scaffold with growth factors, human endothelial cells from liposuctioned fat (top) developed into a network of blood vessels and wrapped around scaffold fibers. A sample 3-D printed scaffold mimics a lower jawbone (bottom).
Both: J. Temple et al/Journal of Biomedical Materials Research 2014

The current challenge is to produce tissue that has its own system of blood vessels to supply nutrients needed for the new bone to grow. In the *Journal of Biomedical Materials Research Part A* in 2014, Grayson's group outlined a method for printing bone grafts with internal pore structures that would allow blood vessels to grow through the graft while maintaining the structure of the scaffold. The team is now investigating ways to help spur such growth by seeding the structure with endothelial cells or blood-vessel forming cells from fat.

Heart-healthy fat cells

Endothelial cells and other cells in fat are the lifeblood of efforts to develop a patch that can be applied to damaged heart tissue following a heart attack. Stuart Williams, a cardiologist at the University of Louisville in Kentucky, is creating a cell-infused patch seeded with a mixture of smooth muscle cells, endothelial cells and blood cells, all obtained from fat tissue.

"This fat tissue contains a huge number of blood vessel–forming cells," Williams says.

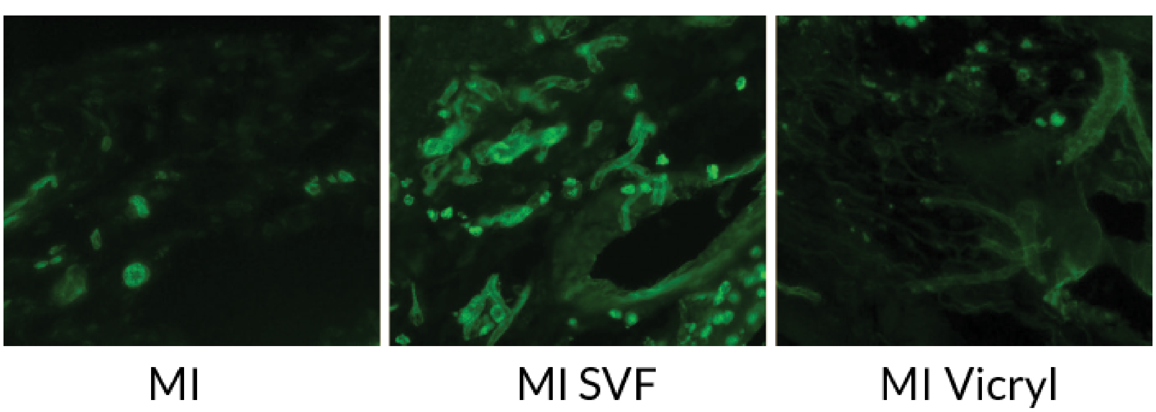
The idea for the patch, outlined in 2013 in *Stem Cells Translational Medicine*, is to harvest fat from a patient, pull out the vessel-forming cells and seed the cells onto a biomaterial that can be immediately implanted. The whole process, from start to finish, will take about an hour.

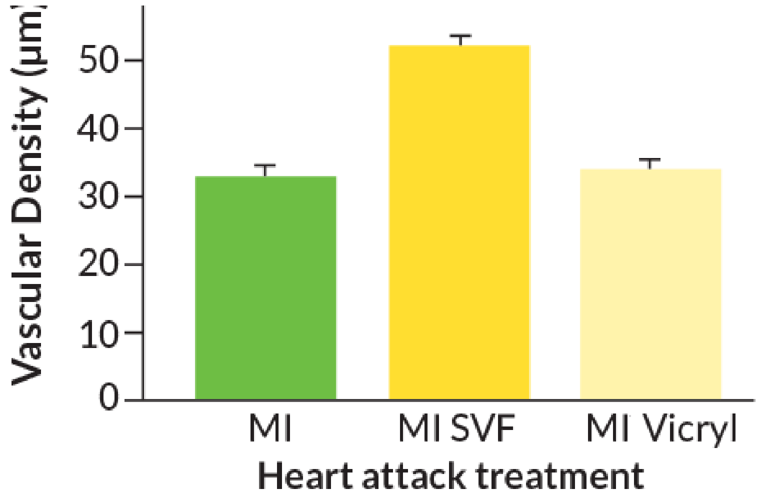
The fat-cell patch works particularly well to promote healing in very small blood vessels, Williams says, a feature that may be especially beneficial for women, who often have more problems with their small blood vessels and fewer problems with the large ones.

Story continues after graph

Repairing heart damage

Rats treated with a patch seeded with endothelial cells from fat tissue two weeks after a heart attack (MI SVF) show more new blood vessels (green) in the damaged area of the heart, compared with untreated rats (MI) and rats treated with an unseeded patch (MI Vicryl). Four weeks after treatment, the MI SVF rats had better heart function and less tissue damage. Total vessel density (vessels per square millimeter) was determined through staining methods.





Source: A.J. Leblanc et al/Stem Cells Translational Medicine 2013

“The interesting thing is, there’s really no stem-ness to these cells at this point,” Williams says. “They don’t have to differentiate. All they have to do is reconnect with each other to form these new blood vessels.”

The patches could be created in the operating room during surgical bypass, he says.

Such patches might also be applied to other areas of the body, such as legs, hands or feet, where patients have limited blood flow, Williams says. In wounds that aren’t healing well, cells could be injected directly into the area to promote blood flow and healing.

While Williams has shown his technology works in animals, he hasn’t yet tested it on people. Getting the federal go-ahead to pursue studies in humans remains a challenge for the heart patch and many other new applications of fat cells.

Current guidelines issued by the U.S. Food and Drug Administration allow trials for treatments in which cells are harvested and injected back into the same patient in a single surgery. But the FDA, and regulatory agencies worldwide, are wrangling with questions on how to test and assess new types of therapies in which cells are grown on scaffolds or manipulated in the lab.

Questions remain, for example, on how to best handle cells in the lab to ensure safety and purity of a product, and how to package and transport products once they are made. Fat stem cells, for example, may change or dedifferentiate when growing in a lab dish, sitting on a warehouse shelf or even following injection into the body, Tuan says.

Later this year, the FDA plans to hold a public hearing to solicit comments from scientists, manufacturers and others on how to proceed. Meanwhile, scientists in the field agree that the potential for fat to do good is here.

“Fat may actually be a natural storehouse of regenerative cells,” Williams says. “When applied correctly, these cells may someday help repair bodies on an as-needed basis.”

This story appears in the March 19, 2016, issue with the headline, "Fat as a fixer."

Citations

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