MedicalXpress

Iron-binding drug could help diabetics heal stubborn wounds

July 27 2009

A drug used to remove iron from the body could help doctors fight one of diabetes' cruelest complications: poor wound healing, which can lead to amputation of patients' toes, feet and even legs.

The drug, deferoxamine, helped diabetic mice heal small cuts 10 days faster than those who did not receive treatment, according to researchers from Stanford University School of Medicine and the Albert Einstein College of Medicine. The team is now working to arrange human trials for deferoxamine. If the results translate, it could help doctors combat such diabetic complications as foot ulcers, an "unmet medical need of gigantic proportions," said Geoffrey Gurtner, MD, professor of surgery and senior author on the paper to be published Monday, July 27, in the Proceedings of the National Academy of Sciences.

"As soon as some more studies are done on its efficacy, it's not going to be difficult to get clinicians to pick [deferoxamine] up," said Richard Clark, MD, a biomedical engineer at Stony Brook University of New York who researches treatments for wound healing and was not involved in the study. "It's quite a significant work."

Blisters, cuts or pressure sores on diabetic patients' lower limbs often heal slowly or not at all, putting patients at risk for infection and amputation. Internal injuries are an issue, as well: More than 40 percent of patients hospitalized for heart attacks have clinical diabetes, and they are less likely to recover fully than their non-diabetic counterparts. The reason, say researchers, is that diabetic tissue fails to reconnect oxygen-

deprived areas to the bloodstream with new vessels. What they didn't know was why the vessels don't form.

Now, Gurtner and colleagues say the culprit is a transcription factor that can't thrive in the high-sugar environment of diabetic tissue. Their potential treatment, deferoxamine, is already Food and Drug Administration-approved for the management of chronic iron-overload disorders.

To tease out a treatment, the researchers first focused on the mechanisms of healing. They isolated fibroblasts, the cells that secrete fibers to heal wounds and bind cells together in an extracellular matrix. Normally, such fibroblasts ramp up production of a protein called vascular endothelial growth factor in response to low oxygen. This factor prompts the formation of new blood vessels. In diabetic cells, however, growth factor production remained flat.

Previous studies suggested that high glucose — a symptom of diabetes — might be to blame. To investigate, the researchers grew healthy fibroblasts in low or high glucose environments for four weeks, mimicking healthy and diabetic tissue. They then exposed the cells to low oxygen.

In response, cells grown in high-glucose ramped up production of growth factor by only 20 percent, compared with 200 percent in cells grown in low glucose. Similar experiments with diabetic and non-diabetic mice confirmed the findings: High glucose was consistently associated with minimal growth factor production in low-oxygen environments.

But what was the glucose doing to hobble growth factor production? The team next looked at hypoxia-inducible factor-1a (HIF-1a), a protein that acts, Gurtner said, as a "second-to-second oxygen sensor" in the cell. When oxygen gets low, HIF-1a binds to DNA to trigger a cellular

response, including production of vascular endothelial growth factor.

To work efficiently, HIF-1a must bind with a molecule called p300. That's where the system broke down, the researchers found. When cells were grown in high-sugar environments, the two molecules decreased their binding by half.

The problem, said Michael Brownlee, MD, a molecular cell biologist at the Einstein College of Medicine in New York and co-author on the paper, is that high glucose inside cells results in the creation of free radicals, which oxidize iron. The iron then interacts with other cellular molecules to form DNA-damaging hydroxyl radicals. That damage causes a cascade of problems, including malformation of the p300 protein. Once damaged, p300 can't effectively bond with HIF-1a.

"What you need to do is interrupt this cascade," Brownlee said.

To do so, the team chose deferoxamine, an off-patent drug that binds to and removes iron from the environment. Experiments in cell cultures suggested that deferoxamine brought hypoxia-inducible factor-1a and p300 back together, but would that translate to better wound healing?

To find out, the researchers gave diabetic mice small cuts. Rodents, unlike people, have a thin muscle layer under their skin that allows them to pull the edges of wounds together. That makes it difficult to compare a mouse's healing process to a human's. To solve this problem, the researchers glued a tiny, washer-shaped stent around the wounds, preventing muscle contraction. They then treated some of the mice with deferoxamine cream.

The results were promising: Mice treated with the drug healed in 13 days, compared with 23 days in untreated mice. Treated mice also produced almost threefold more vascular endothelial growth factor.

"By understanding the science of why is it that diabetics generate wounds more readily and don't heal wounds, we're able to start to target those mechanisms," Gurtner said.

The next step, said Gurtner and Brownlee, is to test the drug on human wounds. Deferoxamine is currently given in the form of an injection and can have side effects ranging from mild stomach upset to, in rare cases, susceptibility to serious bacterial infection. However, in collaboration with Stanford chemical engineer Jayakumar Rajadas, PhD, the team is now developing a dissolvable sheet, similar in consistency to a Listerine breath strip, which could be placed on the wound to deliver the medication. This dressing would keep the dose and side effects low, Gurtner said, as well as making application of the drug less painful for patients.

Source: Stanford University Medical Center (news : web)