

Unraveling how mesenchymal stem cells from gum tissue accelerate wound healing

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Human skin structure. Credit: Wikipedia

Ever notice how a cut inside the mouth heals much faster than a cut to the skin? Gum tissue repairs itself roughly twice as fast as skin and with reduced scar formation. One reason might be because of the characteristics of gingival mesenchymal stem cells, or GMSCs, which can give rise to a variety of cell types.

"This study represents the convergence of a few different paths we've been exploring," says Songtao Shi, chair and professor of Penn Dental Medicine's Department of Anatomy and Cell Biology and the senior author on the study. "First, we know as dentists that the [healing](#) process is different in the mouth; it's much faster than in the skin. Second, we discovered in 2009 that the gingiva contains mesenchymal stem [cells](#) and that they can do a lot of good therapeutically. And, third, we know that mesenchymal stem cells release a lot of proteins. So here we asked, How are the gingival mesenchymal stem cells releasing all of these materials, and are they accelerating wound healing in the mucosal tissues?"

The work appears in the journal *Science Translational Medicine*.

Xiaoxing Kou, a visiting scholar at Penn Dental Medicine, was the first author on the work. Shi and Kou collaborated with colleagues Chider Chen and Anh Le from Penn Dental Medicine as well as Yanheng Zhou from Peking University, Xingtian Xu from the University of Southern California, Los Angeles, Claudio Giraudo and Maria L. Sanmillan from the Children's Hospital of Philadelphia, and Tao Cai from the National Institute of Dental and Craniofacial Research.

From earlier work by Shi's group and others, it was clear that mesenchymal stem cells perform many of their functions by releasing signaling molecules in extracellular vesicles. So to understand what distinguishes mesenchymal stem cells in the gingiva from those in the skin, the Penn-led team began by comparing these extracellular vesicles between the two types. They found that the GMSCs contained more proteins overall, including the inflammation-dampening IL-1RA, which blocks a proinflammatory cytokine. IL-1RA also happens to be used as a therapy to treat rheumatoid arthritis, an inflammatory condition.

Next the team zoomed in to look at what might be controlling the release of IL-1RA and other cytokines. They had a suspect in the protein Fas,

which they had earlier connected to immune regulation. They found that in gingival MSCs had more Fas than skin MSCs, and that mice deficient in Fas had reduced IL-1RA as well as reduced secretion of IL-1RA.

Further molecular probing revealed that Fas formed a protein complex with Fap-1 and Cav-1 to trigger the release of small extracellular vesicles. To identify the connection with wound healing, they examined wound tissue and found that IL-1RA was increased in GMSCs around the margins of wounds. Mice lacking IL-1RA or in which the protein was inhibited took longer to heal gingival wounds.

In contrast, when the researchers isolated IL-1RA that had been secreted from GMSCs and injected it into [wounds](#), it significantly accelerated wound healing.

"We found that mesenchymal stem cells, and especially gingival [mesenchymal stem cells](#), release large amount of cytokines through an extracellular vesicle," says Kou.

These findings may have special significance for people with diabetes, a major complication of which is delayed wound healing. In the study, the researchers found that GMSCs in mice with diabetes were less able to secrete extracellular vesicles compared to GMSCs in healthy mice, and their GMSCs also had less IL-1RA secretion. Introducing extracellular vesicles secreted from the GMSCs of healthy mice reduced wound healing time in diabetic mice.

"Our paper is just part of the mechanism of how these stem cells affect wound healing," Kou says, "but I think we can build on this and use these cells or the extracellular vesicles to target a lot of different diseases, including the delayed wound healing seen in diabetic patients." Moving forward, Shi, Kou and colleagues want to move their work into the clinic.

"We are targeting translational therapies," says Shi. "These cells are easy to harvest from the gingiva, and that makes them a beautiful cell for clinical use. We have a lot of work ahead of us, but I can see using these cells to reduce [scar formation](#), improve [wound healing](#), and even treat many inflammatory and autoimmune diseases."

More information: X. Kou et al., "The Fas/Fap-1/Cav-1 complex regulates IL-1RA secretion in mesenchymal stem cells to accelerate wound healing," *Science Translational Medicine* (2018).
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