Scientists find an important molecular trigger for wound-healing

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Scientists at The Scripps Research Institute have made a breakthrough in understanding a class of cells that help wounds in skin and other epithelial tissues heal, uncovering a molecular mechanism that pushes the body into wound-repair mode.

The findings, which appear in an advance, online version of the *Immunity* on August 16, 2012, focus on cells known as γδ (gamma delta) T cells. The new study demonstrates a skin-cell receptor hooks up with a receptor on γδ T-cells to stimulate wound healing.

"This is a major activation pathway for γδ T cells, and it may be a key to treating slow-wound-healing conditions, such as we see in diabetes," said Scripps Research Professor Wendy L. Havran, senior author of the study. "Chronic non-healing wounds among diabetics and the elderly are an increasing clinical problem."

Rounding and Multiplying

Havran's laboratory specializes in the study of γδ T cells, and the team has produced many of the findings in this research field, including the discovery of these cells' major role in epithelial wound repair. Epithelial tissues are barrier tissues to the outside world, such as skin and the inner surfaces of the gut and lungs.

Normally, γδ T cells reside in these tissues and extend finger-like

projections, called dendrites, that contact neighboring epithelial cells. When injury or infection occurs, the epithelial cells signal their damaged condition to the γδ T cells. In response, the T cells retract their dendrites, become round, start proliferating, and secrete growth-factor proteins that stimulate the production of new epithelial cells in the vicinity—thus helping to repair the wound.

Researchers know of very few interactions between epithelial cells and γδ T cells that are involved in this process. Two, however, are known to be crucial. One of these is through the □□ T cell receptor and the other was described in a 2010 Science paper, whose first author was Havran laboratory Senior Staff Scientist Deborah A. Witherden. But these two interactions don't fully explain the transformation that γδ T cells undergo in the vicinity of wounds. "We've wanted to learn more about the molecules that mediate this dramatic change," Havran said.

Signaling a Transformation

To do that, Witherden identified an antibody that could block keratinocytes' ability to activate γδ T cells in culture. She found that the antibody bound to a keratinocyte surface receptor called plexin B2. She also found that when lab mice have small skin wounds, their injured keratinocytes express more plexin B2 soon after the wounding occurs—pointing to a role for plexin B2 in signaling skin-cell damage.

The next step was to find plexin B2's signaling partner on γδ T cells. "Plexin B2 is very similar to other plexin B family members, including plexin B1, which previously has been shown to bind the CD100 receptor on T cells," said Witherden. "So we thought that perhaps plexin B2 and CD100 can interact as well."

Further tests revealed that plexin B2 and CD100 do indeed bind tightly together; moreover, γδ T cells can't go fully into wound-repair mode

when they lack CD100. Witherden found as well that skin wounds in mice take an extra day or two to heal when the mice don't have this receptor. "This is very similar to what we see in mice that lack γδ T cells altogether," she said.

Removing CD100 from other types of T cells had no effect on wound healing time, indicating that the absence of this receptor specifically on γδ T cells is the reason for the slower healing.

By stimulating CD100 with plexin B2 molecules or even with CD100-binding antibodies, the team showed that this receptor is the principal trigger for the dramatic appendage-retraction and rounding phenomenon seen in γδ T cells after nearby wounds. Without it, the T cells are largely unable to undergo this transformation. "This rounding process seems to be vital for these T cells to function normally in wound healing," said Witherden.

Potential Clinical Significance

In early follow-on work, the team has found evidence that this same plexin B2-CD100 interaction is also needed for the prompt activation of γδ T cells and wound healing in the lining of mouse intestines—which suggests that this receptor helps govern wound healing in epithelial tissues generally.

The finding clearly is important for the basic scientific understanding of T cells and their functions. But it is likely to have medical significance, too. Non-healing wounds affect more than 4 million people in the United States and are the leading cause of amputations. These chronic wounds have a major impact on patient's lives and result in enormous health care costs. "If deficiencies in this γδ T cell activation pathway are even partly responsible, then we may be able to develop drugs to boost this pathway and treat conditions involving chronic non-healing wounds," said

Havran.

The γδ T cell population appears to be involved not just in wound healing, but also in defending against other threats to epithelial tissues. "One of the future directions of our research will be to understand the roles of these molecules in T cell activation pathways in fighting infections and tumors," she added.

More information: "The CD100 Receptor Interacts with Its Plexin B2 Ligand to Regulate Epidermal γδ T Cell Function," *Immunity*, August 16, 2012.

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