Wounded T cells

By Kai-Jye Lou, Staff Writer

Researchers at **The Scripps Research Institute** think they may have uncovered a key reason why chronic wounds are so persistent: functionally impaired epidermal T cells.¹ But before these findings can be translated into a therapeutic, the mechanism underlying the impairment needs to be uncovered.

The Scripps group had previously found hints that certain epidermal T cell populations might be involved in wound healing. In 2002, Wendy Havran showed that mouse epidermal T cells regulate wound repair.² In 2005, her group reported that these cells also regulate skin homeostasis through production of insulin-like growth factor 1 (IGF1).³ Increased levels of IGF1 at a wound site are a hallmark of early-stage repair. However, the involvement of human epidermal T cell populations in the healing process was not known.

In a new paper in *The Journal of Experimental Medicine*, Havran's group translated the rodent results into a human wound repair model. The team not only demonstrated the role of human epidermal T cell populations in wound healing, but also showed that the cells are functionally impaired in chronic wounds.

In human skin cultures, stimulation of the two known epidermal T cell populations— $\alpha\beta$ and $\gamma\delta$ —increased IGF1 levels and accelerated wound closure compared with what was seen in unstimulated controls. Blocking IGF1 signaling with an antibody reversed the increase in wound closure speed.

Most important was the difference in $\alpha\beta$ and $\gamma\delta$ epidermal T cells isolated from patients with acute wounds compared with those from patients with chronic wounds. The former showed an increase in IGF1 production during the tissue repair process and were responsive to stimulation. The latter showed no increase in IGF1 and were less responsive to stimulation.

"This is the first demonstration of the role of epidermal T cell populations in a human wound healing model," said Havran, who is a professor in the Department of Immunology and Microbial Science at Scripps. "People have always wanted to know if the results from mouse wound healing models will translate to humans because the mouse only has a $\gamma\delta$ epidermal T cell population, whereas humans and primates have both $\alpha\beta$ and $\gamma\delta$ epidermal T cells. The really exciting result for us was finding out that epidermal T cell populations in chronic wounds were nonfunctional."

"These findings should have much impact on our understanding of chronic wound persistence, which in the light of Havran's new finding can be perceived as a T cell defect," said Willi Born, a professor in the Department of Immunology at **National Jewish Health** and the **University of Colorado Denver**. "The data also imply that these T cells are in fact a critical source of IGF1 and not just one among several sources."

Thus, Born told *SciBX*, the *JEM* paper "provides convincing evidence for a role of human skin-resident T cells in wound healing."

Therapeutic directions

Unlike acute wounds, the three main types of chronic wounds—diabetic, pressure and venous ulcers—will not heal without constant intervention. Standard care remains a combination of daily dressing changes and devices to remove weight and pressure from the wound site.⁴

The lone biologic on the market is Regranex becaplermin, a gel formulation of recombinant platelet-derived growth factor- β (PDGFB; PDGF- β) sold by **Johnson & Johnson** to treat diabetic foot ulcers. Last June, however, J&J updated the product's label to include a black box warning of an increased risk of cancer in patients treated with three or more

tubes of Regranex.

Another approach is wound debridement, in which dead, damaged or infected tissue is surgically removed to promote the healing potential of the remaining healthy tissue.

Medical devices such as skin substitutes have also been approved for chronic wounds.

"There is a lot of interest in identifying new ways to treat patients with chronic wounds," said Havran. The results in the *JEM* article "support the idea of developing strategies to reactivate epidermal T cells or transplanting these cells from healthy regions of the body into the chronic wound. I would see treatment strategies based off these findings complementing current wound treatment strategies."

Born said it was "very encouraging that the human skin-resident T cells behave similarly to mouse skin-resident T cells." However, he added that the findings of the Scripps team "are largely derived from studies *in vitro*. It is difficult to predict from such studies what might be found *in vivo*."

If the findings do translate to the clinic, Born thinks the result could be more specific wound treatments that avoid the side effects of less-targeted approaches. "T cells can be targeted specifically because they express cell-surface molecules that are not found on other cells in the skin," he said.

For example, Born noted that skin-resident T cells are sensitive to mitogens and cytokines that have no effect on keratinocytes.

Rebecca O'Brien, also a professor in the Department of Immunology at National Jewish Health and the University of Colorado Denver, noted that T cell-targeting approaches still would need to avoid

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The Scripps Research Institute

stimulating $\alpha\beta$ and $\gamma\delta$ T cell populations elsewhere in the body because of the potential for undesirable immune responses. She suggested that localized T cell stimulation with a topical formulation such as a cream may be feasible.

Mechanisms before therapies

Before the results in *JEM* can be translated into therapeutics, researchers contacted by *SciBX* wanted to see additional studies that elucidate the function of epidermal T cells and the mechanism by which they become impaired in chronic wounds.

"In mouse models, we were able to show that the $\gamma\delta$ epidermal T cells are major contributors to the wound healing process, but at this point we still don't know how important the $\alpha\beta$ and $\gamma\delta$ epidermal T cell populations are in humans," Havran told *SciBX*. "We still don't know if just targeting these epidermal T cell populations is enough to promote healing of chronic wounds in humans."

She added: "We certainly expect that epidermal T cells are not the only functionally impaired cell types in the chronic wound environment."

Both Born and O'Brien also wanted to see additional studies that elucidate and compare the function of human $\alpha\beta$ epidermal T cells with the function of $\gamma\delta$ cells.

Havran said the key next steps for her group will be to identify a phenotype that distinguishes functional cells from impaired cells and to discern the mechanism behind the impairment. "We want to know if there are cell-surface markers that distinguish responsive T cells from unresponsive T cells," she said.

Indeed, Havran thinks the development of epidermal T cell-based

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therapies for chronic wounds hinges on understanding why they become functionally impaired.

"If it happens to be the case that these cells are exhausted and just won't respond anymore, then transplanting cells from another part of the body may be a viable approach. We may be able to isolate functional T cells from healthy parts of the body, activate them *ex vivo*, and then transplant them to the site of the chronic wound," she said. "If they are

functionally impaired for some other reason, however, then we may be able to develop strategies or compounds that reactivate these T cell populations in the chronic wound."

Scripps has not disclosed the patent and licensing status of the *JEM* findings.

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COMPANIES AND INSTITUTIONS MENTIONED

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