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Scientists discover 'switch' critical to wound healing

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Patients with diseases such as diabetes suffer from painful wounds that take a long time to heal, making them more susceptible to infections that could even lead to amputations. A*STAR's discovery paves the way for therapeutics to improve healing of such chronic wounds, which are a significant burden to patients.

Scientists from A*STAR's Institute of Medical Biology (IMB) have identified a molecular "switch" that controls the migration of skin cells necessary for wounds to close and heal. This is especially significant for diabetics and other patients who suffer from chronic wounds, wounds that do not heal or take years to do so, which are vulnerable to infections and could lead to amputations. This switch mechanism may hold the key to developing therapeutics that will reduce or prevent chronic wounds.

The scientists discovered that a tiny "micro-RNA" molecule, called miR-198, controls several different processes that help wound healing, by keeping them switched off in healthy skin. When skin is wounded, the manufacture of miR-198 quickly stops and the levels of miR-198 drop, switching on many wound healing processes.

In the non-healing wounds of diabetics, miR-198 does not disappear and wound healing remains blocked. This therefore identifies miR-198 as a potential diagnostic biomarker for non-healing wounds. These findings were recently published in the prestigious journal *Nature*.

Chronic wounds in patients with diabetes are a major global health

burden and the most common cause of lower extremity amputations. In Singapore, diabetes is the fifth most common medical condition diagnosed and one in nine people aged 18 to 69 has diabetes. Unfortunately, chronic wounds are currently poorly understood and insufficiently treated. Chronic wounds also tend to affect the elderly and disabled patients, especially those confined to a wheelchair or bed-bound.

"Moving forward, we hope to translate this research into improved patient outcomes. We can now build on this research, to see how we can modulate the defective switch in chronic wounds by targeting miR-198 and its interacting molecules, to develop new strategies for treating chronic wounds," principal investigator at IMB and lead author of the paper, said. "Our research provides a comprehensive understanding of the mechanism of the wound healing process."

Professor Birgitte ane, Executive Director of IMB, said, "This switch appears to be an entirely new regulatory component in wound healing, and probably a very important one. Poor wound healing is a major healthcare burden, and this discovery is particularly timely in the face of aging populations and the sharp global rise in diabetes. The finding gives us a platform from which to develop therapies that could significantly reduce chronic wounds and improve healthcare."

An FSTL1-miR-198 molecular 'see-saw' switch

The information necessary to expressmicroRNA-198 (miR-198) and follistatin-like 1 (FSTL1) protein are found in a single "message" produced by the cell. However, miR-198 and FSTL1 protein cannot be produced at the same time – it can only be one or the other. These two molecules also have opposite roles: miR-198 (found in unwounded skin) inhibits skin cell migration and wound healing, whereas FSTL1 protein (expressed after injury) promotes skin cell migration and wound healing.

A regulatory switch dictates their expression, and hence controls the "see-saw" between inactive resting skin cells and the cell migration necessary for wound healing.

Dr. Sampath and her team showed that healthy unwounded skin contained high levels of miR-198 but no FSTL1 protein. They demonstrated that these high levels of miR-198 prevent skin cell migration by suppressing several genes, such as PLAU, LAMC2 and DIAPH1[4], which are needed for different aspects of the wound healing process. However upon injury, miR-198 is switched off in the wound by a signal from transforming growth factor β1 (TGF-β1). This allows FSTL1 to now be made instead, and the skin migration genes to be unblocked, promoting migration of skin cells into the wound area to drive skin wound healing.

The scientists further examined skin samples of chronic non-healing ulcer wounds from patients with diabetes mellitus. They observed that, unlike healthy skin that had been injured, there remained high levels of miR-198 (inhibiting skin cell migration and wound healing) and an absence of FSTL1 protein (promoting skin cell migration upon wounding), indicating that this "switch" is defective in chronic wounds.

More information: Sundaram, G. et al. See-saw' expression of microRNA-198 and FSTL1 from a single transcript in wound healing, *Nature*, February 10, 2013. doi:10.1038/nature11890

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