Linking wound healing and cancer risk

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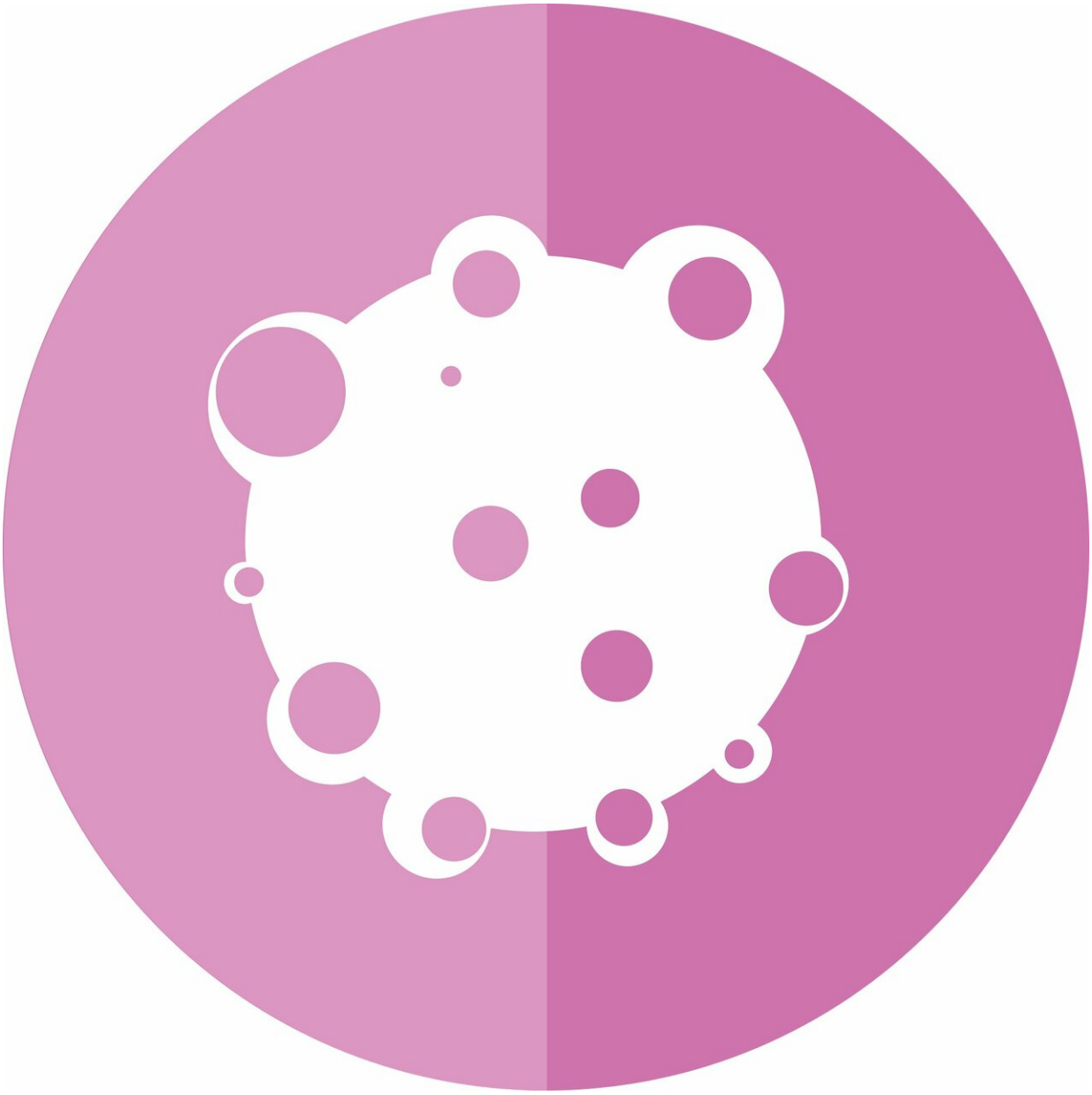

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When our skin is damaged, a whole set of biological processes springs into action to heal the wound. Now, researchers from the VIB-UGent Center for Inflammation Research have shown that one of the molecules involved in this, HMGB1, slows down wound healing. It is, however, also essential for tumor formation at sites of previous injury. The researchers found that HMGB1 controls the actions of neutrophils, a specific type of immune cells, in skin wounds and that this is crucial for cancer initiation. Targeting this pathway could be beneficial in diabetic wound care and in patients suffering from skin blistering diseases. Their work appears in *Cell Reports*.

NETting wounds

Wounding initiates a complex repair mechanism that is aimed at fast regeneration of the injured tissue. A large amount of clinical data shows that chronic inflammation or previous injury can predispose tissues to tumor formation, a hypothesis already stated in the nineteenth century.

However, it is still not fully understood what the molecular mechanisms are that link injury repair to cancer. The first immune cells that enter the skin after injury are neutrophils, short-lived immune cells that form specialized structures termed NETs (neutrophil extracellular traps) in skin wounds.

Skin wounds and cancer risk

Dr. Esther Hoste, first author of the study, and colleagues in the group of prof. Geert van Loo (VIB-UGent Center for Inflammation Research) investigated the role of the molecule HMGB1 in injury repair and tumor initiation in the skin. HMGB1 is a molecule that is secreted by damaged

tissue and activates the immune system. The scientists genetically deleted HMGB1 from skin cells in mice and showed that their wounds healed faster than normal mice and that they are completely protected from wound-induced tumor formation.

Mice lacking HMGB1 from epithelial skin cells showed reduced neutrophil numbers and NETs in skin wounds. Dr. Hoste explains: "We demonstrated that a mechanism used to alarm your immune system that something is going wrong, can be hijacked for cancer initiation. While secretion of HMGB1 is a good thing in conditions of minor injury, it can be a harmful event in more serious or chronic wounds as it can trigger tumor formation at these wound sites. This really is a case of 'too much of a good thing can hurt you.'"

The harmful NETs that link wound repair to tumor formation were also observed in patients suffering from the severe blistering disease Recessive Dystrophic Epidermolysis Bullosa. These patients undergo repetitive cycles of injury and repair and are at high risk to develop skin cancer.

Faster healing, without cancer

The findings strongly suggest that targeting HMGB1 release or NET formation in the skin might be of interest in blistering diseases or in diabetic patients suffering from chronic ulcers. Such HMGB1-focused therapies could accelerate wound healing responses, while limiting the risk of cancer initiation.

"We were surprised that interfering with the secretion of one molecule provided such benefits to the injury repair process and could completely block tumor formation. We now want to investigate whether this newly identified molecular pathway also affects other tissues where trauma is linked to tumor formation, such as the intestine. We are currently

working on new ways to inhibit this detrimental pathway in order to bring our findings to the clinic," says prof. Geert van Loo.

More information: Hoste et al. Epithelial HMGB1 delays skin wound healing and drives tumor initiation by priming neutrophils for NET formation, *Cell Reports* 2019 DOI: 10.1016/j.celrep.2019.10.104

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