REG3A defect caused by hyperglycemia delays wound healing in diabetes

Subject Code: H10

With the support by the National Natural Science Foundation of China, National Key Research and Development Program of China, and National Program for Support of Top-Notch Young Professionals, the research team led by Prof. Lai Yuping (赖玉平) at Shanghai Key Laboratory of Regulatory Biology, School of Life Sciences, East China Normal University, uncovered a critical role of regenerating islet-derived protein 3-alpha (REG3A) in control of dysfunctional immune responses to promote wound healing in diabetes, which was published in *Nature Communications* (2016, 10(7): 13393).

Diabetes is known as one of the major public health concerns, and is the fourth leading cause of death in the world. In 2016, an estimated 422 million adults were living with diabetes, and the incidence of diabetes in China is 9.4%. Among these patients, 15% individuals are under the risk of foot problems such as diabetic ulcers, which are usually caused by delayed wound healing after acute injury. To develop therapeutics for treatment with these patients, a comprehensive and decent understanding of the pathogenesis of delayed or unhealed wounds in diabetes is needed.

It is known that a well-controlled and coordinated balance between immune defense, epithelial cell proliferation and differentiation is essential to normal wound repair. Before they obtained the breakthrough in the study of REG3A in control of dysfunctional immune responses to promote wound healing in diabetes, Yuping Lai's group had shown that REG3A was induced by interleukin-17 (IL-17) in keratinocytes, and acted back to regulate keratinocyte proliferation and differentiation to promote wound healing. This finding was published in *Immunity* (2012, 37(1): 74—84) as a highlighted story.

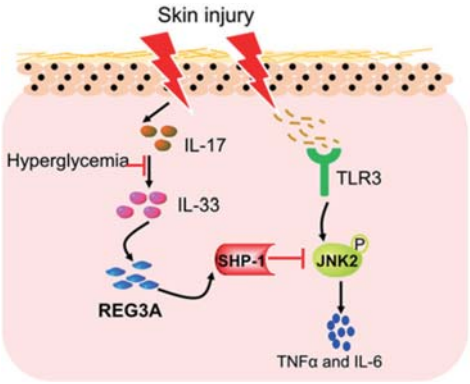

Figure The schematic graph reflects the interaction between REG3A and TLR3 signaling.

However, in diabetes diminished keratinocyte proliferation and migration are observed in chronic non-healing wounds. They thereby hypothesized that impaired non-healing wounds of diabetes might correlate with the aberrant expression of REG3A. As expected, they observed that REG3A expression was impaired in skin wounds of diabetes, and the defective REG3A expression led to excessive production of pro-inflammatory cytokines and impaired wound healing in diabetes. More importantly, they discovered that the reduction of cutaneous REG3A was a consequence of decreased IL-17-induced IL-33 caused by hyperglycemia, and further delineated the mechanism of REG3A in the inhibition of Toll-like receptor 3 (TLR3)-mediated inflammatory responses via the induction of the negative regulatory factor Src homology region 2 domain-containing protein tyrosine phosphatase 1 (SHP-1), which exhibited a major role in delayed wound healing by inhibiting TLR3-activated c-Jun N-terminal kinase 2 (JNK2) phosphorylation. Specifically, they further determined that the capacity of REG3A to control TLR3-induced inflammation and its effect on keratinocyte proliferation are critical, but irreplaceable, for normal wound healing responses in diabetes. Altogether, these findings reveal that the aberrant expression of REG3A amplifies inflammation in diabetic skin wounds and may be a previously unknown key element in the pathogenesis of delayed or unhealed wounds of diabetic individuals. Both findings were published in *Nature Communications* and *Immunity* papers implicate the potential of REG3A as a therapeutic target in wound healing.