# The Roles of MicroRNAs in Skin Wound Healing

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**Xi Li defended her PhD thesis on February 8, 2019 at Karolinska Institutet, Stockholm, Sweden. The opponent was Professor Marjana Tomic-Canic, from Department of Dermatology and Cutaneous Surgery, University of Miami, USA and Principal supervisor was Ning Xu Landén, Department of Medicine Solna, Unit of Dermatology and Venereology, Karolinska Institutet, Stockholm, Sweden. The dissertation is available at: https://openarchive.ki.se/xmlui/handle/10616/46604**

Skin is an essential biological barrier of the human body, and wound healing is the fundamental physiological process to keep its integrity. Chronic non-healing wounds are growing socioeconomic and health concerns, which longs for more understanding of their pathophysiology to discover effective treatments. In this thesis, we focused on how microRNAs (miR) work together with their target protein-coding genes to regulate the complex wound healing process, and by exploring the roles they play in chronic wounds we aimed to discover potential therapeutic targets.

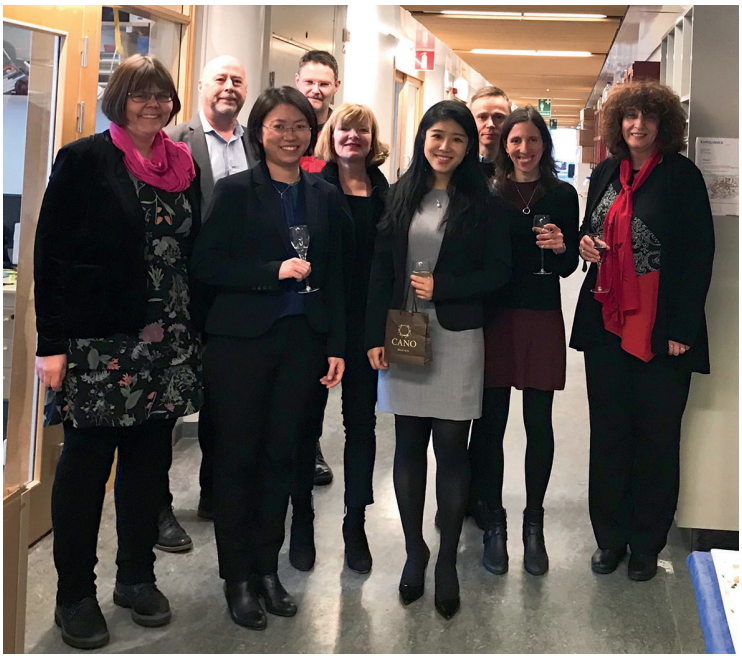

*Fig. 1.* From left: Lena Eliasson (examination board), Gunnar Kratz (examination board), Ning Xu Landén (principal supervisor), Ole E Sørensen (examination board), Mona Ståhle (co-supervisor), Xi Li (defendent), Andor Pivarcsi (co-supervisor), Enikö Sonkoly (Co-supervisor) and Marjana Tomic-Canic (Opponent).

In paper I, a distinct up-regulation of miR-31 in human acute wounds was identified from profiling analysis. We discovered miR-31 as a pivotal regulator in promoting keratinocyte proliferation and migration by targeting EMP1 during wound healing, emphasizing its importance in re-epithelialization.

In paper II, miR-34 family, as a famous tumour suppressor, popped out amidst the top upregulated miRs in venous ulcer. *In vitro*, miR-34a and miR-34c enhanced inflammatory response of epidermal keratinocytes via targeting LGR4 and positively regulating NF-κB signalling pathway. *In vivo*, mouse model of either miR-34 local overexpression or Lgr4 knockout displayed impaired wound healing with excessive inflammation and suppressed cell growth. These suggest that miR-34 plays a pathological role in chronic wounds by contributing to the excessive inflammation.

In paper III, in continuity with our previous report that miR-132 displays anti-inflammatory and pro-proliferative roles in keratinocytes, we studied the function of miR-132 in another major skin resident cell type fibroblasts. By both overexpression and inhibition, miR-132 was proved to facilitate migration of primary human dermal fibroblasts, through targeting RASA1 and regulating Ras signalling. Since fibroblasts derived from chronic wounds are non-migratory, our study suggests the miR-132-RASA1-Ras axis with potential therapeutic impact.

In paper IV, we tested the therapeutic potential of miRs, taken miR-132 as an example. A significant downregulation of miR-132 was revealed in diabetic foot ulcer. Intradermal injection of liposome-encapsulated miR-132 mimics effectively accelerated wound healing. Moreover, *ex vivo* human model exhibited ameliorated re-epithelialization upon miR-132 topical application, denoting that local treatment of miR-132 deserves

further evaluation in a clinical trial as a potential target for treating chronic wounds.

Conclusively, this thesis investigated the crucial functions of miR-31, miR-34 and miR-132 in different phases of normal skin wound healing process and in chronic wounds, and pointed out a promising potential of microRNA-based therapy in treating chronic wounds.

**List of original publications**


1. Li D, Li X, Wang A, Meisgen F, Pivarcsi A, Sonkoly E, et al. MicroRNA-31 promotes skin wound healing by enhancing keratinocyte proliferation and migration. J Invest Dermatol 2015; 135: 1676–1685.
2. Wu J, Li X, Li D, Ren X, Li Y, Herter EK, et al. MicroRNA-34 family enhances wound inflammation by targeting LGR4. Manuscript
3. Li X, Li D, Wikström JD, Pivarcsi A, Sonkoly E, Ståle M, et al. MicroRNA-132 promotes fibroblast migration via regulating RAS P21 protein activator 1 in skin wound healing. Sci Rep 2017; 7: 7797.
4. Li X, Li D, Wang A, Chu T, Lohcharoenkal W, Zheng X, Grünler J, et al. MicroRNA-132 with therapeutic potential in chronic wound. J Invest Dermatol 2017; 137: 2630–2638.