# Editorial commentary:
# Wanted: MicroRNAs to the aid of the diabetic foot

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Wound healing is complex and involves several interconnected phases, including hemostasis, inflammation, proliferation, maturation and remodeling. Healthy skin is crucial for human body integrity. It is the largest organ system of the body, protecting against mechanical forces, fluid imbalance, thermal dysregulation and infections. Over time, diabetes induces critical alterations in the skin, including imbalances in the wound healing phases. In normal skin injury, acute inflammatory responses are initiated, beginning with recruitment of neutrophils, monocytes, and mast cells to the site of injury. Besides significant alteration in expression of inflammatory cytokines, such as TNF- α, IL-6, IL-8 and growth factors coordinating wound repair, diabetes can also cause alterations in skin insulin action, crucial for maintenance of glucose and lipid homeostasis. In contrast to healthy acute wounds, wound healing in diabetic patients does not progress correctly due to peripheral neuropathy, macro- and micro-vascular disease, impaired angiogenesis and chronic inflammation often with persistent infection. Controlling skin inflammation improves diabetic wound healing.

Diabetes worldwide has assumed epidemic proportions with over 650 million diabetics predicted by 2040. Diabetic foot ulceration (DFU) is a severe complication occurring in about 20% of diabetes patients, requiring intensive care, often resulting in hospitalizations and even amputations for its management, thus it represents a serious public health problem. Moreover, about 58% of clinically treated ulcers are infected, and the progression from DFU to diabetic foot infection is present in 85% of amputation cases highlighting the importance of integrated treatments. The cost of treatment in the US in 2001 was about 11 billion dollars. Importantly, if multidisciplinary treatments are implemented, amputations can be decreased by 49–85%. Therefore, development of an effective treatment for chronic DFU is imperative.

Neuropathy and/or diminished vascular perfusion are serious risk factors for DFU development. However, infection control is difficult due to diminished local blood flow, and systemic antibiotics may not reach infected ulcers in suitable concentrations. Local anti-infection or immune-modulatory treatments constitute an important, yet underutilized, strategy for treatment of diabetic wounds.

In this issue of the Journal, Ozdemir and Feinberg present a comprehensive review on the pathophysiological roles of microRNAs (miRNA) in diabetic wound healing and describe opportunities for their therapeutic use. In brief, miRNAs are small non-coding RNA molecules controlling protein levels by post-transcriptional action. Recently, miRNAs have been recognized as important regulators of glucose metabolism, and their altered expression and function has been linked to loss of glucose homeostasis, leading to pathogenic conditions, including diabetes. They are also important players in wound healing under diabetic conditions, as described by Ozdemir and Feinberg and others. All phases of wound healing are affected by miRNAs and they have been shown to be altered in diabetes. Of special interestis the observation that specific sets of miRNAs are involved in acute and chronic inflammation (‘inflammiRs’).

These inflamemiRs include miR-146a, miR-155, miR-15-b-5p, miR-132, miR-191 and miR-200 family members, also important in wound healing, but this list is not exhaustive and more miRNAs are likely regulated by acute and/or chronic inflammation. Because it is possible to improve diabetic wound healing by controlling skin inflammation at least in mouse models, the obvious question is whether these miRNAs can be employed in an immune modulatory fashion to improve diabetic wound healing? In addition, miRNAs may work in clusters and not individually as many studies have so far evaluated. Furthermore, the notion that molecules work together in a concerted way to regulate processes, such as metabolism, cellular immunity, inflammation and wound repair is not new; however it is a new fact that exosomes, small extracellularvesicles, can regulate cell to cell cross-talk and all of these functions due to their specific cargo. Exosomes have been used in wound healing, a promising new technology, that carry not only miRNAs but also small bioactive molecules, including peptidesand proteins that together can better contribute to immunemodulation, inflammation and tissue repair.

Interestingly, new studies point to the regulation of miRNAs by host microbiota. This could be important in DFU pathogenesis, because DFUs are colonized and a majority of chronic wounds are infected with pathogens. Microbes extensively communicate with the host immune system and modulate host miRNA expression in the gut and brain, but how the microbial composition interacts with miRNA during wound healing is not well established. Data indicate that miRNAs, including miR-15b-5p, miR-146, miR-155, miR-125, and miR-21, can be affected during bacterial infection and may contribute to immune responses. It is therefore intriguing to think that by manipulating wound local microbes one could potentiate healing via modulation of miRNA expression. In addition, another important idea that needs furtherinvestigation is the fact that bacterial small RNAs may significantly regulate human genes in ways that could alter host cellular processes involved in wound healing.

Furthermore, a major limitation of many studies concerningmiRNA action in wound healing is the use of mouse models forwound healing. There are several important differences between wound healing in mice and humans: Mice heal by contraction of the epidermis, while human wounds close by granulation tissue. The stem cell niches of mouse and human dermis are different, as well as both the normal and pathogenic microbiota. Moreover, the microbial composition of DFUs is highly heterogeneous, whereas mouse models by nature of being models are very homogenous, which may limit translatability. Although miRNAs are evolutionarily highly conserved, a primate specific miRNAs was described as having an important role in wound healing of humanskin. Thus, mice and humans may have different sets of miRNA involved in cutaneous wound healing. Even though miRNAs may be conserved in sequence and regulation between mouse and human skin, it is important to consider that the target mRNAs, upon which miRNAs act, are far less likely to be conserved. Additionally, mouse wounds are for the most part acute wounds, while human DFUs are normally chronic wounds having persistent inflammation, and which do not follow the standard time course of cellular and molecular events that leads towards the healing of a healthy acute wound. Finally, healing of a DFU depends to a high degree of pressure off-loading. If the ulcer is sufficiently off-loaded,healing will often occur (although slowly), while the DFU under perpetual pressure will not heal.

Mouse wound healing models are inadequate by not being under pressure. These limitations to the use of mice for wound healing studies also impede the identification of mechanisms important for human wound healing, and, in particular, healing of DFUs. Thus, studies should be performed in human skin models and in tissue or samples from diabetic patients in order to validate miRNA findings obtained in mice and translate these into useful clinical treatment.