Circulating MicroRNAs Link Inflammation to Impaired Wound Healing in Diabetes

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Soon after their discovery in 1993, it became clear that microRNAs (miRs) regulate virtually all cellular processes. Since then, many miRs have been described to coordinate gene expression programs in the context of cardiovascular disease, including diabetes mellitus. MiRs usually perform their duties intracellularly, but interest in extracellular miRs as biomarkers or intercellular messengers has risen recently. In the cardiovascular system, it has been shown that miRs can travel between endothelial cells, smooth muscle cells, cardiac fibroblasts, and cardiomyocytes, thereby affecting gene expression in recipient cells. Next to their role in intercellular communication, circulating miRs were also shown to be powerful biomarkers for various cardiovascular conditions. In this issue of *ATVB*, Dangwal et al show that miR-191 is both a circulating biomarker for type-2 diabetes mellitus and an intercellular messenger with a potent effect on wound healing.

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Using miR microarrays, the authors were able to identify several miRs that are differentially detectable in the plasma of patients with type-2 diabetes mellitus compared with healthy controls. These miRs include miR-191 and miR-200b. Interestingly, the reduction of miR-191 in plasma of patients with type-2 diabetes mellitus was also seen by Zampetaki et al. However, Dangwal et al also noticed that the presence of chronic wounds essentially reversed the extracellular levels of miR-191 in the circulation. Rather than dismissing this seemingly contradictory finding, the authors set out to investigate the meaning of this observation.

What the groups of Tschoepe and Thum found is that inflammatory stimuli that are present in wound fluid induce the secretion of miR-191 by endothelial cells. This finding could explain the observation that miR-191 increases in type-2 diabetes mellitus patients with wound healing complications, compared with type-2 diabetes mellitus patients without wounds. The authors then went on and tested whether miR-191 may have a functional effect in endothelial cells and dermal fibroblasts that would potentially show a role of miR-191 in wound healing in diabetic conditions. Indeed, this was the case because the authors showed that secreted miR-191 can be taken up by other endothelial cells and dermal fibroblasts. In recipient cells, miR-191 impaired angiogenesis, migration, and apoptosis by targeting the tight junction protein ZO-1 (Figure 1). Because ZO-1 has been shown to be essential for migration, miR-191-mediated downregulation could very well explain the migration and angiogenesis defects observed after overexpression of miR-191. As all miRs are capable of targeting multiple target mRNAs, it is likely that other factors contribute to the effects of miR-191. Evidence that this is indeed the case comes from the observation that miR-191 has effects beyond regulation of migration, namely apoptosis induction. Which target mRNAs are involved in this remains to be seen, but it is clear that the effects of miR-191 on apoptosis are cell context–dependent because miR-191 was shown to inhibit apoptosis in hepatocellular carcinoma.

Although these findings provide evidence for functional transfer of miR-191 from endothelial cells to other endothelial cells and fibroblasts, the study also highlights a limitation of the use of miR-191 as biomarker for type-2 diabetes mellitus. Even though miR-191 is reproducibly reduced in plasma of type-2 diabetes mellitus patients, patients with wound healing problems have the same plasma miR-191 levels as healthy controls. Finally, the study by Dangwal et al shows another interesting example of how miRs travel from one cell to another to crucially affect the gene expression pattern and phenotype of the recipient cells with potent effects on wound healing. These types of cell–cell communication are now becoming widely established in the field, and in the...
future, even more diverse forms of cell–cell communication in
the cardiovascular and other systems will undoubtedly be dis-
covered. Furthermore, the study also opens up possibilities to
potentially treat chronic wounds in diabetes mellitus patients.
As the skin is an easily accessible organ and the potency of
anti-miRs has been proven extensively, even in clinical trials,\textsuperscript{15}
inhibition of miR-191 promises to be a feasible strategy to
enhance wound healing in patients with diabetes mellitus.

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