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Spatiotemporally-Tunable double-layered microneedle confers immunoregulation to improve wound healing in diabetes

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Introduction
Impaired wound healing and ulcer complications are a major cause of disability and mortality in diabetic patients, often associated with reduced physical function and diminished quality of life. The underlying mechanism involves dysregulated macrophage plasticity, in which macrophages fail to transition from a proinflammatory to a reparative state, along with impaired angiogenesis, collectively leading to non-healing wounds. There is a pressing clinical need for advanced treatment strategies to promote diabetic wound healing.

Materials and Methods
Microneedle (MN) patches represent an effective approach for transdermal drug delivery, and recent research has focused on developing smart systems capable of sensing and responding to the pathological wound microenvironment. Using single-cell RNA sequencing, we identified a persistent proinflammatory state in macrophages and disrupted cellular crosstalk between macrophages and endothelial cells in diabetic wounds.
To address these abnormalities, we designed a novel double-layered microneedle patch that co-encapsulates reactive oxygen species (ROS)-responsive nanoparticles containing IL-33 and glutathione (GSH)-responsive nanoparticles loaded with Roxadustat (Rox). This integrated nanoplatform enables programmed and sequential drug release in response to the wound microenvironment, thereby promoting macrophage polarization and angiogenesis in a spatially and temporally controlled manner.

Results
In diabetic mouse models, the MN patch significantly improved wound healing by modulating local immune responses and enhancing tissue repair. Specifically, it facilitated the transition of proinflammatory macrophages to an anti-inflammatory phenotype and robustly stimulated angiogenesis. RNA sequencing analysis of wound macrophages further revealed that Ddit4 expression was upregulated following treatment and played a key functional role in regulating macrophage polarization and promoting vascularization.

Conclusions
By combining a macrophage modulator (IL-33) and an angiogenesis inducer (Rox) within a smart microneedle system, we achieved simultaneous immune normalization and enhanced angiogenesis. This strategy provides a promising and comprehensive technology for the treatment of diabetic wounds, with improved efficacy, safety, and patient compliance.