Hypoxia and H_2O_2 Dual-Sensitive Vesicles for Enhanced Glucose-Responsive Insulin Delivery

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Statement of Purpose: Diabetes mellitus is a chronic disease associated with elevated glucose in the blood, which currently affects 415 million people worldwide.[1] The traditional exogenous insulin injection does not closely match the physiological release of insulin, often resulting in inadequate glycemic control and subsequent consequences such as limb amputation, blindness and kidney failure.

Methods: Here we report a glucose-responsive insulin delivery device utilizing vesicles sensitive to both hypoxia and H_2O_2 (*d*-GRPs) (Figure 1). A local hypoxic environment can be quickly generated due to the oxygen consumption during the enzymatic conversion of glucose to gluconic acid, which facilitates the solubility switch of the polymer through the bioreduction of nitroimidazole groups[2] on the side chains. Moreover, the thioether moiety within the designed polymer not only responds to H_2O_2,[3] the byproduct during glucose oxidation, to promote the disassembly of vesicles, but also eliminates the excess H_2O_2 to maintain the activity of GOx and circumvent the damage to skin tissue. Furthermore, the *d*-GRPs can be integrated within a microneedle (MN)-array patch to achieve convenient, painless and continuous administration of insulin.

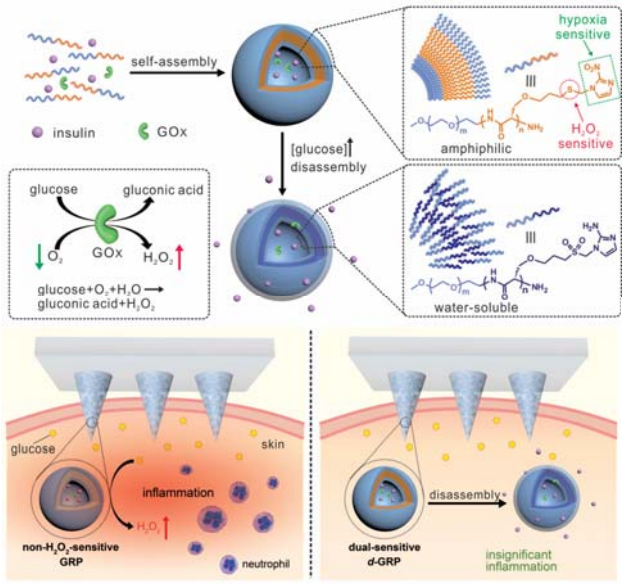

Figure 1. Schematic of hypoxia and H_2O_2 dual-sensitive polymersome-based vesicles loading microneedle-array patches.

Results: The amphiphilic hypoxia and H_2O_2-sensitive polymer can self-assemble into a nano-scaled bilayer vesicles structure. *In vitro* studies showed a fast insulin release from *d*-GRPs was achieved under a hyperglycemic state. Furthermore, the undesirable H_2O_2 could be effectively scavenged by the thioether moieties in polymers. *In vivo* experiment in a chemically induced type 1 diabetic mouse model demonstrated this smart insulin patch could maintain the blood glucose level at a normal range without any long-term side effect (Figure 2).

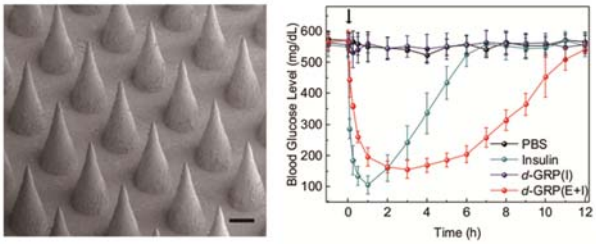

Figure 2. Left: A SEM image of MNs array. Scale bar is 200 μm. Right: *In vivo* studies of the MN-array patches for type 1 diabetes treatment: blood glucose levels in streptozotocin-induced diabetic mice after treatment with blank MNs containing only crosslinked HA, MNs loaded with human recombinant insulin, MNs loaded with d-GRPs containing insulin and enzyme (d-GRP(E+I)), or MNs loaded with d-GRPs containing insulin (d-GRP(I)).

Conclusions: An effective glucose-responsive insulin delivery strategy based on hypoxia and H_2O_2 dual-sensitive vesicles was developed for diabetes treatment without long-term side effect. Additionally, this dual-sensitive formulation strategy displays the potential benefit in controlled delivery for other therapeutic agents under hypoxia and high oxidative stress.

References:

[1] Ran M. Chem Soc Rev. 2014; 43: 3595-3629.
[2] Jicheng Y. Proc Natl Acad Sci. 2015; 112: 8260-8265.
[3] Napoli A. Nat Mater. 2004; 3:183-189.