ENGINEERING ANTIOXIDANT AND OXYGEN-RELEASING LIGNIN HYDROGEL COMPOSITES TO ACCELERATE WOUND HEALING

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Keywords: Biomaterial, Fibrosis, Wound Repair, Lignin-based

Background: Impaired wound healing and scar formation have far-reaching socioeconomic effects. Excessive reactive oxygen species (ROS) cause oxidative stress in the wounds and delay healing by hampering vascularization and promoting inflammatory macrophage and myofibroblast differentiation resulting in increased inflammation and scarring. Engineered biomaterials capable of scavenging ROS and facilitating controlled release of oxygen can circumvent the challenge of oxygen diffusion in situ to promote cell infiltration and survival, which is not achieved with current biomaterials. We hypothesize that the application of novel lignin (an antioxidant from lignocellulose)-based composites with ROS-scavenging and oxygen-releasing properties will enhance neovascularization and attenuate inflammation to promote wound healing.

Materials/Methods: We photo-crosslinked thiolated lignosulfonate (TLS) in methacrylated-gelatin (GelMA) via thiol-ene chemoselective ligation. We developed calcium peroxide(CPO)-incorporated lignosulfonate microparticles, where the dissociation of CPO into oxygen is facilitated by lignosulfonate, and added them to the GelMA-TLS composites. 6mm wounds were made in wild-type mice using silicone stents to prevent contraction and divided into 4 groups: Untreated(UNTX), GelMA-TLS(TLS), GelMA-TLS with carriers with/without oxygen release capacity(CPOc,CPO). Wounds were harvested at 7d and examined for epithelial gap, granulation tissue(H&E), endothelial cells and vessels(CD31), and macrophages(CD206). Data presented as mean+SD, n=3-6wounds/group; p-value by ANOVA.

Results: Morphometric wound analysis showed treated wounds had greater granulating tissue with marked increase in CPO (UNTX-1.3+0.9mm2; TLS-2.1+0.8; CPOc-2.7+0.4; CPO-2.5+-0.4,$p<0.05$). Notably, the CPO matrix showed infiltration and integration with a granulating tissue. Both CPOc and CPO wounds had greater vessel density (UNTX-14.0+4.7lumens/40x field; TLS-18.9+3.9; CPOc-27.9+7.2; CPO-25.2+7.6,$p<0.05$). The CPOc and CPO wounds had fewer macrophages (UNTX-32.7+12.4%cells/40 field; TLS-24.9+14.3; CPOc-14.6+4.4; CPO-19.3+5.5,$p<0.05$).

Conclusions: Our data showcases the synergistic antioxidation and oxygen production capacity of lignin composites improved wound healing associated with reduced inflammation and enhanced neovascularization, representing new potential therapeutics for attenuating fibrosis and improving wound healing with engineered biomaterials.

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