1551965

Affinity Binding Alginate Biomaterial for the Sustained Delivery of Cardiovascular-Protective Proteins

Ruvinov, E[1]; Leor, J[2]; Cohen, S[2]
[1]Ben-Gurion University of the Negev, Beer-Sheva, Israel; [2]Tel-Aviv University and Sheba Medical Center, Tel-Hashomer, Israel

Background and Aims: We developed a novel injectable alginate biomaterial that affinity-binds and presents, at a sustained manner, a variety of heparin-binding proteins, in a similar fashion to extracellular matrix. Here, we aimed to test whether the sustained delivery of hepatocyte growth factor (HGF) from such system would enhance its therapeutic properties.

Methods and Results: Mass spectrometry showed that the affinity-binding of HGF to alginate-sulfate protects HGF from proteolysis. When the bioconjugate was incorporated in alginate hydrogel (creating the affinity-binding hydrogel), HGF release rate was significantly slower compared to conventional hydrogel(*p*, interaction<0.0001, two-way ANOVA). The released HGF maintained bioactivity as confirmed by ERK1/2 activation as well as protection from apoptosis induced by H_2O_2, in cardiac cell cultures ($p<0.05$ vs. control). In rat MI model, the affinity-binding hydrogel significantly prolonged HGF tissue retention and bioavailability, compared to unmodified hydrogel or soluble HGF ($p<0.0001$, F test). Importantly, sustained delivery of HGF significantly improved tissue blood perfusion in mice hindlimb ischemia model, as compared to saline, soluble-HGF and empty alginate (41.5±1.7% vs. 26.3±3.1% vs. 19.3±3.2% vs. 27.5±3.0%, respectively; $p<0.05$ compared to saline), evaluated by Laser Doppler. Compared with saline, soluble-HGF and empty alginate, HGF in affinity-binding alginate significantly increased blood vessel density (41.4±2.3 vs. 18.9±1.2 vs. 25.7±.2 vs. 23.8±2.1 vessels/mm^2, respectively; $p<0.05$), evaluated by ב-smooth muscle actin staining.

Conclusions: Bioconjugation with alginate-sulfate resulted in protection, prolonged tissue exposure and increased availability of HGF in hostile environments, such as the ischemic heart and limb. The prolonged factor action induced angiogenesis in severe limb ischemia model, suggesting the use of this system as a promising approach for cardiovascular regenerative therapy.