LIPID-POLYMER NANOCARRIERS FOR CARTILAGE REGENERATION

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Introduction

Musculoskeletal ailments caused by cartilage damage are common, and thanks to more and more modern diagnostic methods, more and more often recognized. Moreover, cartilage diseases progress with age and are a consequence of injuries, becoming a dominant problem in orthopedic surgery. The conducted research aims to produce conjugates for cartilage regeneration based on chondrogenic differentiation of mesenchymal stem cells isolated from Wharton's jelly (hUC-MSC).

Materials and Methods

Kartogenin (KGN) – an active substance – was encapsulated in the liposomes. The carriers were covered with modified hyaluronic acid (Hy) or chondroitin sulfate (Ch) in order to obtain better stability of the systems. Ch was modified by octadecyl groups at two different substitution degrees, 15% and 30% (ChC18_15 and ChC18_30). Hy was modified by dodecyl or octadecyl groups at a similar substitution degree of 7% (HyC12 and HyC18). The physicochemical analysis of the obtained systems was carried out by dynamic light scattering, zeta potential, and fluorescence measurements. The thermotropic behavior of lipid membranes was studied using a Nano DSC calorimeter (TA Instruments). HUC-MSC morphology imaging after incubation with the prepared formulations and metabolic toxicity test were performed. Additionally, these systems have been tested to differentiate stem cells into chondrocytes using real-time PCR (rt-PCR).

Results and Discussion

Hy and Ch substitution by alkyl domains were confirmed by XPS spectra. KGN was successfully incorporated into the lipid bilayer. Composed formulations were stabilized by covering their surfaces with Hy and Ch derivatives. The changes in thermograms for an aqueous dispersion of DPPC confirmed the incorporation of polymers' hydrophobic domains into the lipid bilayer. Moreover, an increase in the liposome size and decrease in the ζ-potential values confirmed the presence of polymers on liposomes surfaces (FIG. 1). Despite both systems: modified GAGs and liposomes with KGN have high negative values, they interact with each other because of the hydrophobic effect. According to cytotoxicity results (MTT assay), all polymers used in lipid formulations were significantly non-toxic than pure polymers. This may be that the hydrophobic anchors are hidden in the lipide bilayer and their exposure to the cell surface is minimized. The selected genes expression was analyzed by real-time PCR. FIG. 2 shows only a couple of formulations. As can be seen, a lower dosage of liposomes with KGN that HyC18 coats give the best differentiation results. All systems have induced Col1A1 and SOX9 gene expression compared to untreated cells.

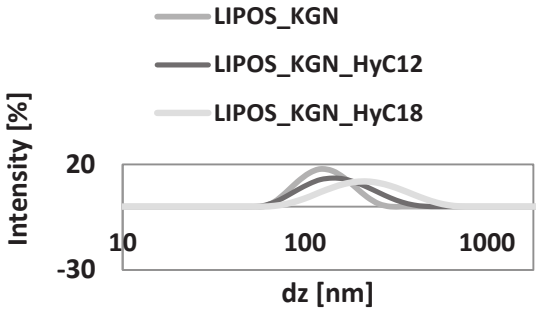

FIG. 1. DLS size distribution profiles of bare liposomes with KGN and coated with HyC12 or HyC18.

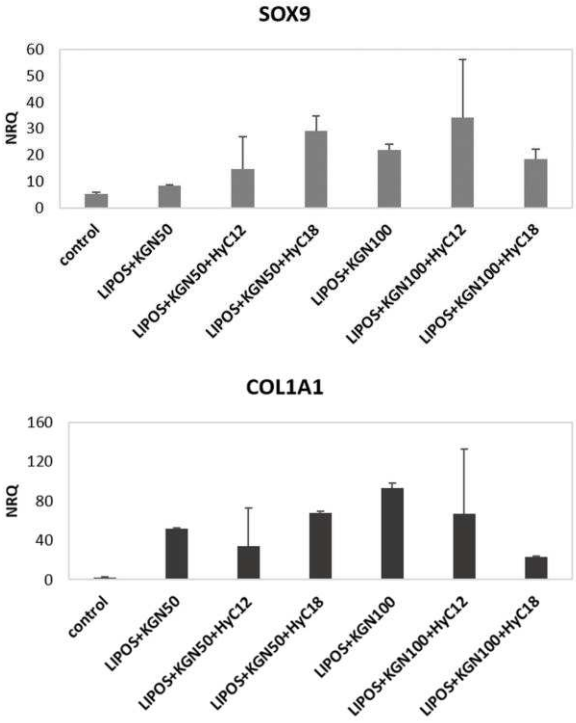

FIG. 2. Cartilage markers expression after stimulation by selected formulations, compared to control (untreated hUC-MSC).

Conclusions

Composed hybrid lipid-polymer formulations are stable vesicles as carriers of KGN. The resulting systems are promising conjugates for the regeneration of cartilage tissue.

Acknowledgments

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