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Design of Synthetic Extracellular Matrices of Liver Tissue Engineering

서 석 진

한스바이오메드(주)

Liver tissue engineering encompasses several approaches to develop temporary extracorporeal liver support techniques, such as bioartificial liver (BAL) devices.However, when removed from the architectural liver, hepatocytes rapidly lose liver-specific functions and viability. Thus, selecting and modifying the biomaterials are very important in designing the synthetic extracellular matrix (ECM) for liver tissue engineering. The hydrogel is an appealing scaffold material because it structurally acts as an ECM in tissue engineering. Of these, alginate (AL) scaffolds have recently been developed for liver tissue engineering, due to their biocompatibility and hydrophilicity. However, AL scaffold systems without cell adhesion molecules are able to discourage protein adsorption due to highly hydrated anionic surface. Thus, AL scaffold systems should be modified to promote cell attachment via the molecules related with cell adhesion. Carbohydrate-recognized binding of hepatocytes to matrices has been used for liver tissue engineering.

In this study, xyloglucan (XG) or galactosylated chitosan (GC) with galactose residues recognized by asialoglycoprotein receptors (ASGPR) on hepatocytes was introduced into the AL scaffold system to improve cell adhesion and to maintain viability in culture, and heparin having high affinity for hepatocyte growth factor (HGF) was introduced into AL/GC sponge for stable long-term culture. Hepatocytes exclusively adhered to XG or GC surface compared to polystyrene or chitosan surface, respectively, as controls, indication of specific interaction between galactose residues of XG or GC and ASGPR on hepatocytes.Optimal concentration of XG (0.5 mg/ml) in AL/XG microcapsule, or GC (1 wt.% to AL content) and/or heparin (6 wt.% to AL content) in AL/GC sponge induced maximal liver-specific activities causedby hepatocyte spheroids, resulting from rapid expression of intercellular

adhesion molecules including connexin (Cx) 32 and E-cadherin. Cell aggregation without gap junction intercellular communication (GJIC) does not perform the liver-specific functions for long periods by treatment with a GJIC blocker, 18-glycyrrhetinic acid. The presence of HGF enhanced albumin secretion in AL/GC/heparin sponge compared to that in AL/GC sponge. Coculture of hepatocytes in AL/GC/heparin sponges with NIH3T3 in a transwell insert resulted in significant increase of liver-specific functions, such as albumin secretion rates, ammonia elimination rates, and ethoxyresorufin-O-deethylase activity by cytochrome P4501A1, compared to those in hepatocyte monoculture. These findings suggest that design of a synthetic ECM for hepatocytes as stable spheroids is necessary for primary hepatocytes to perform the enhanced functions in liver tissue engineering.