Hepatic stellate Cells in Liver Fibrosis

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Hepatic stellate cells (HSCs) are localized in perisinusoidal space of liver. In fibrotic liver, they lose lipid droplets containing vitamin A, change to myofibroblast-like phenotype and acquire increased proliferation activity. They also become synthesizing relatively large amount of matrix components including fibrillar collagens, what is called the “activated” state. In addition to type I and type III collagens, we detected that type IV and type XVIII collagens were synthesized by HSCs. These basement membrane collagens were reported to be the precursors of endogenous angiogenesis inhibitors.

We have investigated the treatment for liver fibrosis based on the concept of targeting “activated” hepatic stellate cells by introducing “non-activated” state or apoptosis. Vitamin E molecules are well known as antioxidants, however, recent research developments demonstrated that they possess powerful cholesterol lowering, platelet adhesion inhibition and anti-cancer properties. In this study, four tocopherols and tocol lacking methyl groups attached to the chromanol ring were applied to the “activated” hepatic stellate cells and examined the effects on proliferation activity of HSCs. Rat HSCs were prepared by collagenase perfusion and the “activated” state was induced by culture in vitro. Among four tocopherols and tocol, relatively high proliferation inhibition effects were detected in delta-tocopherol and tocol. Furthermore, cell detachment and apoptosis via anoikis were observed in delta-tocopherol treated and tocol treated cells in a dose response manner. The expression of alpha-smooth muscle actin, a marker for the activated HSCs, was significantly decreased in the treatment groups. These data suggest that vitamin E offers the promising treatment for liver fibrosis and cirrhosis.

CD44 is a type-I membrane glycoprotein abundantly expressed in tumor cells and bind various extracellular matrix (ECM) components such as hyaluronan (IA) and chondroitin sulfates (CS). During tumor cell invasion, HA is degraded into small oligosaccharides by hyaluronidases produced by the tumor cells. We have shown that such HA oligosaccharides induce the proteolytic cleavage of CD44 from tumor cells and promote tumor cell migration in a CD44-dependent manner. We also found that chondroitin sulfate E (CSE), another component of the tumor ECM, strongly enhances CD44 cleavage and tumor cell motility when degraded into oligosaccharides. CSE can also be degraded by hyaluronidas, CSE and its degradation products are detected in pancreatic ductal adenocarcinoma. In CD44-expressing pancreatic tumor cells, degraded forms of CSE but not intact CSE enhanced CD44 cleavage; enzymatic digestion of such low-molecular weight CSE (LMW-CSE) abrogated this enhancement. Among the LMW-CSE preparations examined, 3-kDa CSE most potently induced CD44 cleavage. NMR analysis showed that the 3-kDa-CSE bound to CD44 and that blocking such binding abrogated the CD44 cleavage induction. LMW-CSE also induced prominent filopodia formation and cytoskeletal changes in tumor cells; these effects were also abrogated by blocking the LMW-CSE binding to CD44. Chemically synthesized CSE hexasaccharides also enhanced the CD44 cleavage and tumor cell motility in a CD44-dependent manner. Thus, the degraded forms of CSE modulate cell adhesion and migration by interacting with tumor-cell CD44. These results strengthen the hypothesis that tumor cells and the surrounding ECM act on each other reciprocally, to promote tumor progression. They also indicate that tumor-cell CD44 plays a crucial role in these interactions by recognizing a non-HA ECM degradation product, LMW-CSE, directly implicating LMW-CSE in CD44-mediated tumor progression.

References