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Fusion protein of retinol binding protein and albumin domain III reduces liver fibrosis

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Liver fibrosis is the excessive accumulation of extracellular matrix including collagen. Activated Hepatic Stellate Cells (HSCs) are major producer of fibrotic neomatrix, playing a key role in the fibrogenesis and inactivating HSCs has been considered a promising therapeutic approach. We previously showed that albumin is endogenously expressed in quiescent HSCs and that its expression inhibits HSC activation. For stellate cell targeting, albumin (domain III) was fused to C-terminus of Retinol Binding Protein (RBP) and the resulting recombinant fusion protein (referred to as R-III) was found to be incorporated into cultured HSCs in a STRA6 (a membrane receptor for RBP) dependent manner and inactivate HSCs. Our mechanistic study showed that Retinoic Acid (RA) signaling is involved in HSC activation and that R-III treatment or albumin expression down regulates its signaling through direct binding to RA, which likely contributes to the anti fibrotic effect. RA receptor agonist and retinaldehyde dehydrogenase overexpression abolished the anti fibrotic effect of R-III and albumin respectively. In animal experiments, injected R-III via tail vein was found to be localized predominantly in HSCs in liver indicating that RBP functions as a targeting domain. Importantly, R-III administration reduced liver fibrosis induced by carbon tetrachloride (CCl_4) or bile duct ligation (BDL) by 35%, which was accompanied with decreased immunostaining of α-smooth muscle actin, a marker of myofibroblasts. It also exhibited a preventive effect against CCl_4 inducd liver fibrosis. Our *in vitro* studies, together with our *in vivo* observations suggest that R-III is a good candidate as a novel anti fibrotic drug.

Biography

Junseo Oh has completed his PhD from Kyoto University and Post-doctoral studies from NIH/NCI, MD. He is currently working as a Professor in the Department of Biomedical Science, Korea University Graduate School. His research interests include extracellular matrix remodeling, tumor invasion and tissue fibrosis.

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