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Fucose-appended dendrimer/α-cyclodextrin conjugate as a novel NF-κB decoy carrier to Kupffer cells infulminant hepatitis mice induced by lipopolysaccharide

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Fulminant hepatitis is a serious, life-threatening disorder and is associated with inflammatory cytokines produced by Kupffer cells. However, a number of clinical trials for the treatment of fulminant hepatitis did not show enough substantial benefits. Since NF-κB is a key mediator of inflammatory response in Kupffer cells, NF-κB decoy would be an attractive candidate for the treatment of fulminant hepatitis. Recently, Opanasopit et al. revealed that fucosylated protein is preferentially taken up by Kupffer cells via a fucose receptor (Fuc-R). Therefore, the fucosylation to NF-κB decoy carrier is one of the prominent approaches for Kupffer cell-selective delivery. We recently reported that thioalkylated mannose-modified star burst polyamidoamine (PAMAM) dendrimer/α-cyclodextrin conjugates (Man-S-α-CDE (G3)) has the potential for a novel antigen presenting cell-selective siRNA carrier [1]. However, there is no report on fucose-appended α-CDE as a Kupffer cell-selective NF-κB decoy carrier. Therefore, in the present study, we newly synthesized fucosyl-oxypropyl-thio-propionylated α-CDE(Fuc-S-α-CDE (G2) (Fig. 1A)) and evaluated the potential of Fuc-S-α-CDE (G2)/NF-κB decoycomplex for the treatment of fulminant hepatitis [2].

Fuc-S-α-CDE (G2, average degree of substitution of fucose (DSF) 2)/NF-κB decoy complex significantly suppressed nitric oxide and tumor necrosis factor-α (TNF-α) production from lipopolysaccharide (LPS)-simulated NR8383 cells, a rat alveolar macrophage cell line, by adequate physicochemical properties and fucose receptor-mediated cellular uptake. Intravenous injection of Fuc-S-α-CDE (G2, DSF2)/NF-κB decoy complex

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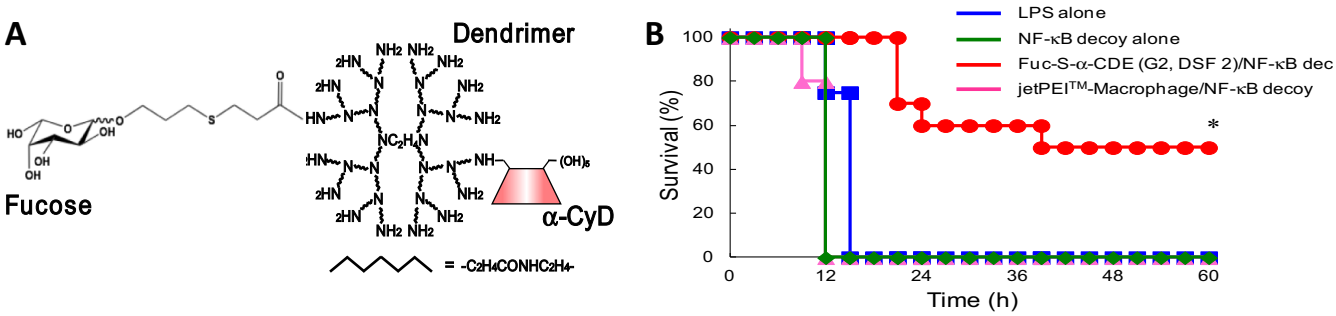

Fig. 1 – Chemical structure of Fuc-S-α-CDE (G2)(A) and effects of Fuc-S-α-CDE (G2, DSF2)/NF-κB decoy complex on survival curve of fulminant hepatitis mice induced by LPS. Each line represents the survival of 4–10 mice. *P < 0.05 versus LPS alone (B).

extended the survival of LPS-induced fulminant hepatitis model mice, compared to those of NF-κB decoy alone and jetPEI™-Macrophage/NF-κB decoy complex (Fig. 1B). In addition, Fuc-S-α-CDE (G2, DSF2)/NF-κB decoy complex administered intravenously highly accumulated in the liver, compared to naked NF-κB decoy alone. Furthermore, the liver accumulation of Fuc-S-α-CDE (G2, DSF2)/NF-κB decoy complex was inhibited by the pretreatment with $GdCl_3$, a specific inhibitor of Kupffer cell uptake. Also, the serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and TNF-α levels in LPS-induced fulminant hepatitis model mice were significantly attenuated by the treatment with Fuc-S-α-CDE (G2, DSF2)/NF-κB decoy complex, compared with naked NF-κB decoy alone. Taken together, these results suggest that Fuc-S-α-CDE (G2, DSF2) has the potential for a novel Kupffer cell-selective NF-κB decoy carrier for the treatment of LPS-induced fulminant hepatitis in mice.

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