Chondroitin 4-O-sulfotransferase-1 Modulates Wnt-3a Signaling Through Control of E Disaccharide Expression of Chondroitin Sulfate

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Wnt-3a is a ligand that activates the β-catenin-dependent pathway in Wnt signaling, which is implicated in numerous physiological events such as morphogenesis. So far, heparan sulfate (HS) proteoglycans have been highlighted as a low-affinity receptor for morphogens containing Wnts. Here we show the importance of chondroitin sulfate (CS) proteoglycans in the efficient signaling of Wnt-3a and the structural features of CS required for the regulation of Wnt-3a signaling. Wnt-3a signaling was depressed in a mouse L cell mutant called sog9 which is defective in the EXT1 gene encoding the HS-synthesizing enzyme and chondroitin 4-O-sulfotransferase (C4ST-1) gene compared with parental L cells. The transfection of sog9 cells with C4ST-1 resulted in the recovery of Wnt-3a signaling, while the expression of EXT1 in sog9 cells could not restore Wnt-3a signaling. In addition, the expression level of introduced C4ST-1 correlated with the recovery of Wnt-3a signaling accompanied by the increased expression of the E disaccharide unit of CS. Interestingly, molecular interaction analyses using Biacore revealed that squid CS-E (rich in the E disaccharide unit) strongly bound to Wnt-3a to the same extent as heparin from bovine lung. In contrast, other CS isoforms as well as HS isolated from bovine kidney showed little binding activity to Wnt-3a. Moreover, exogenously added CS-E potently inhibited the accumulation of β-catenin induced by Wnt-3a. These results suggest that CS-E-like structures synthesized by C4ST-1 participate in Wnt-3a signaling and modulate the physiological events caused by Wnt-3a signals.