Synopsis of Original Research Paper

Regulation of Melanin Production by Glycosyltransferases.

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The biological roles of asparagine-linked oligosaccharides (*N*-glycans) on glycoproteins are thought to be played through the interaction of terminal glycan structures and their receptors. The diversity and avidity of the terminal structures are, however, regulated by the core structure of *N*-glycans. In vertebrates, six different *N*-acetylglucosaminyltransferases (GnT-I through GnT-VI) are involved in initiating the synthesis of highly branched *N*-glycan core structure. Among them, we have purified and cloned four GnTs (GnT-III, IV, V, VI) for the first time. GnT-VI catalyzes the transfer of *N*-acetylglucosamine (GlcNAc) to position 4 of the Man α1,6 arm of the core structure of *N*-glycan, forming the most highly branched pentaantennary glycans with a bisecting GlcNAc. The human GnT-VI-homolog (hGnT-VIh) gene was originally identified in the region commonly deleted in pancreatic cancer, but its function is unknown. hGnT-VIh shows no GnT-VI activity, although its primary structure is very similar to that of chicken GnT-VI (galGnT-VI) (50% identity). In order to elucidate the biological role of chicken GnT-VI and human GnT-VIh, the *galGnT-VI* and *hGnT-VIh* genes were introduced into a mouse melanoma cell line B16F1. Melanin production was enhanced in *hGnT-VIh* gene-introduced cells, accompanied by increased tyrosinase activity. In contrast, it was reduced in *galGnT-VI* transfectants, accompanied by a decrease of tyrosinase activity level. To investigate the molecular mechanism of these phenomena, tyrosinase mRNA levels in the cells were examined. The mRNA level in *hGnT-VIh* transfectants was elevated, while that in *galGnT-VI* transfectants was reduced compared to control cells. To study alterations in carbohydrate chains induced by the expression of *hGnT-VIh* and *galGnT-VI* genes, oligosaccharides on cell-surface were examined by flowcytometry using DSA and L-PHA lectins, which recognize poly *N*-acetyllactosamin and β1,6GlcNAc branch, respectively. The reactivity against DSA and L-PHA was increased in hGnT-VIh-transfectants but decreased in *galGnT-VI*-transfectants. Taken together, it is suggested that the expression of the *hGnT-VIh* and *galGnT-VI* genes regulates melanin production via the regulation of tyrosinase expression accompanied by alterations in carbohydrate chain structures.