Core Fucosylation Regulates Epidermal Growth Factor Receptor-mediated Intracellular Signaling*

Received for publication, October 5, 2005, and in revised form, November 2, 2005. Published, JBC Papers in Press, November 29, 2005, DOI 10.1074/jbc.M510893200

Xiangchun Wang‡, Jianguo Gu‡, Hideyuki Ihara‡, Eiji Miyoshi‡, Koichi Honke§, and Naoyuki Taniguchi†

From the ‡Department of Biochemistry, Osaka University Graduate School of Medicine, Japan and the †Department of Molecular Genetics, Kochi University Graduate School of Medicine, Kohasus, Oko-cho, Nankoku, Kochi 783-8505, Japan

α1,6-Fucosyltransferase (Fut8) catalyzes the transfer of a fucose residue to N-linked oligosaccharides on glycoproteins via an α1,6-linkage to form core fucosylation in mammals. We recently found that disruption of the Fut8 gene induces severe growth retardation and early postnatal death. To investigate the molecular mechanism involved, we have established embryonic fibroblasts of Fut8−/− and Fut8+/−, derived from wild-type and Fut8-null mice, respectively. Interestingly, the epidermal growth factor (EGF)-induced phosphorylation levels of the EGF receptor (EGFR) were substantially blocked in Fut8−/− cells, compared with Fut8+/− cells, while there are no significant changes in the total activities of tyrosine phosphorylation of the extracellular signal-regulated kinase (ERK) or c-Jun N-terminal kinase (JNK) activation. In Fut8−/− cells, the expression level of EGFR was significantly reduced by treatment with some glycosidases, and the inhibition of EGFR phosphorylation was significantly suppressed in Fut8−/− cells. Consistent with this, EGFR-mediated JNK or ERK activation was significantly suppressed in Fut8−/− cells. Finally, we found that the core fucosylation of N-glycans is required for the binding of the EGF to its receptor, whereas no effect was observed for the expression levels of EGFR on the cell surface. Collectively, these results strongly suggest that core fucosylation is essential for EGFR receptor-mediated biological functions.

The remodeling of cell surface growth factor receptors by modification of their oligosaccharide structures is associated with certain functions and biological events (1−5). N-Glycans play an important role in the folding, stability, and sorting of glycoproteins (6, 7). They have a core structure, and their branching patterns are determined by glycosyltransferases (8−10).

α1,6-Fucosyltransferase (Fut8) catalyzes the transfer of a fucosyl moiety from GDP-fucose to the innermost GlcNAc residue of hybrid and complex N-linked oligosaccharides on glycoprotein via α1,6-linkage to form core fucosylation in mammals, as shown in Fig. 1. The enzymatic products, core fucosylated N-glycans are widely distributed in a variety of glycoproteins (11) and are altered under some pathological conditions. For example, the level of core fucosylation is elevated in both liver and serum during the process of hepatocarcinogenesis (12). The presence of core fucosylation of α-fetoprotein, a well known tumor marker for hepatocellular carcinoma (HCC), is known to distinguish patients with HCC from those with chronic hepatitis and liver cirrhosis (13, 14). It has recently been reported that the deletion of the core fucose from the IgG1 molecule enhances antibody-dependent cellular cytotoxicity activity by up to 50–100-fold (15, 16) and therefore is thought to have considerable potential for use in antibody therapy against cancer.

Epidermal growth factor receptor (EGFR)-mediated cellular responses to EGF and transforming growth factor-α (TGF-α) stimulation regulate several biological functions including cell growth and cell differentiation. The binding of these ligands to the extracellular domain of EGFR induces activation of its intrinsic tyrosine kinase activity, leading to the receptor autophosphorylation and the phosphorylation of tyrosine residues in various cellular substrates, many of which serve as intracellular signal molecules (17−19). The extracellular domain of EGFR contains 12 potential N-glycosylation sites (20), and the remodeling of N-glycans on EGFR can modulate EGFR-mediating functions (21−26). It has been reported that the binding of EGF to EGFR was significantly reduced by treatment with some N-glycosylation inhibitors (21). In addition, EGF binding as well as its tyrosine kinase activity was reduced by addition of certain lectins (22−24), indicating that N-glycans are required for ligand binding. On the other hand, the overexpression of N-acetylgalactosaminyltransferase III (GnT-III), a pivotal glycosyltransferase that plays a major role in the biosynthesis of hybrid and complex types of N-linked oligosaccharides (27), significantly reduces the ability of EGF to bind to its receptor, EGFR autophosphorylation, and subsequently blocks EGFR-mediated ERK phosphorylation in U373 MG glioma cells (25) or PC12 cells (26). Thus, N-linked oligosaccharides on EGFR appear to be important factors for receptor function. However, to date the roles of core fucosylation in EGFR-mediating functions have not been identified yet.

To investigate the physiological functions of the core fucose, we generated Fut8-null mice. Disruption of Fut8 induces severe growth retardation, early death during postnatal development, and emphysema-like changes in the lung (28). We found that, in mice, a lack of core fucose leads to abnormal lung development and a marked down-regulation of the TGF-β1 signaling pathway. This signaling dysregulation induces the expression and activation of several matrix metalloproteinases, which contributes to the destructive emphysema-like phenotype observed in core fucose-deficient mice. In the present study, we demonstrated that EGFR as well as PDGF receptors are plausible factors that may be responsible for the growth retardation, since a down-regulation in EGFR receptor-mediated signaling could be observed in both Fut8-null cells and mice. Furthermore, reintroduction of the Fut8 gene to Fut8-null cells potentially rescued EGF and the PDGF receptor-mediated signaling impaired in null cells.

EXPERIMENTAL PROCEDURES

Cell Lines—The embryonic fibroblasts derived from wild-type and Fut8-null mice were described (28).

‡ This work was supported in part by the Special Coordination Funds for Promoting Science and Technology and the 21st Century Center of Excellence Program from the Ministry of Education, Culture, Sports, Science and Technology of Japan. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

§ To whom all correspondence should be addressed. Tel.: 81-6-6879-3421; Fax: 81-6-6879-3429; E-mail: jgu@biochem.med.osaka-u.ac.jp.

The abbreviations used are: Fut8, α1,6-fucosyltransferase; HCC, hepatocellular carcinoma; EGF, epidermal growth factor; EGFR, EGF receptor; GnT-III, N-acetylgalactosaminyltransferase III; ERK, extracellular signal-regulated kinase; JNK, c-Jun NH2-terminal kinase; PDGF, platelet-derived growth factor; PABA, 4-(2-pyridylamino)butylamine; PBS, phosphate-buffered saline; PVDF, polyvinylidene difluoride; BSA, bovine serum albumin; AAL, aleuria aurantia lectin; LCA, lens culinaris lectin.
Fut8 Is Needed for the Function of EGFR

**Fut8 Activity Assay**—The specific activity of Fut8 was determined using a synthetic substrate, 4-(2-pyridylamino)butylamine (PABA)-labeled oligosaccharide as a substrate. Cells grown to subconfluence were washed with PBS(−) once, and the cell pellet was suspended in 200 μl of lysis buffer containing 10 mM Tris-HCl, pH 7.4, 150 mM NaCl, and 1% Triton X-100. The cell lysate was then assayed for Fut8 activity as described previously (29).

**Western Blot Analysis**—Cells were solubilized in 1% Triton X-100 lysis buffer (20 mM Tris-HCl, pH 7.4, 10 mM EGTA, 10 mM MgCl2, 1 mM benzamidine, 60 mM β-glycerophosphate, 1 mM Na2VO4, 20 mM NaF, 2 μg/ml aprotonin, 5 μg/ml leupeptin, 0.1 mM phenylmethylsulfonyl fluoride) and then centrifuged at 15,000 × g for 15 min. The supernatants were collected, and protein concentrations were determined using a protein assay BCA kit (Pierce). Equal amounts of protein were run on 10% SDS-PAGE under reducing conditions and then transferred to PVDF membranes (Millipore Corp.). The membranes were probed with anti-EGFR, anti-phospho-ERK1/2 or anti-phospho-JNK1/2 antibody (Cell Signaling, Beverly, MA). Immunoreactive bands were visualized using an ECL kit (Amersham Biosciences). These membranes were stripped and reprobed with an antibody against the corresponding total protein ERK1/2 (Cell Signaling) and JNK1 (Santa Cruz Biotechnology, Santa Cruz, CA) to confirm equal loading.

**Lectin Blotting Analysis**—Whole cell lysate or immunoprecipitated EGFR was subjected to 10% or 7.5% SDS-PAGE and transferred to PVDF membranes (Millipore Corp.). The blots were probed with anti-phospho-ERK1/2 or anti-phospho-JNK1/2 antibody (Cell Signaling and JNK1 (Santa Cruz Biotechnology, Santa Cruz, CA) to confirm equal loading.

**Immunoprecipitation**—Cell lysate (~1 mg of protein), prepared as described above, was incubated with the anti-EGFR antibody (Upstate Biotechnology, Lake Placid, NY) overnight at 4 °C with gentle rocking and then added to 20 μl of protein G-Sepharose (50% slurry) (Amersham Biosciences) for another incubation of 2 h at 4 °C. For homogenate, whole 18.5-day embryos were homogenized in lysis buffer, and the resulting cell lysate was then immunoprecipitated with the anti-EGFR antibody as described above. The immunoprecipitated proteins were visualized using Vectastain ABC kit and ECL kit.

**Cell Surface Biotinylation**—Cell surface biotinylation was performed as described previously (30). Briefly, cells were rinsed twice with ice-cold PBS and then incubated with ice-cold PBS containing 0.2 mg/ml sulfo-NHS-LC-biotin (Pierce) for 1 h at 4 °C. After incubation, the cells were washed three times with ice-cold PBS and solubilized in lysis buffer, and the resulting cell lysate was then immunoprecipitated with the anti-EGFR antibody as described above. The immunoprecipitated proteins were visualized using Vectastain ABC kit and ECL kit.

**In-blot Phosphatase Assay**—Dephosphorylation of EGFR was examined by an In-blot phosphatase assay described previously (31). Cell lysates (~20 μg) of A431 cells treated with 10 ng/ml EGF for 5 min were subjected to SDS-PAGE and electrotransferred on PVDF membrane. Each membrane slice was incubated with or without 0.5 ml of Fut8+/+ or Fut8−/− cell lysates at the indicated concentrations in 30 °C for 1 h. Phosphorylated EGFR was detected with anti-phosphotyrosine.

**Flow Cytometric Analysis**—Cells in subconfluent condition were harvested using 0.2% EDTA and centrifuged at 1000 rpm for 5 min. The cell pellets were suspended in PBS(−) (5 × 10⁶ cells) and incubated with lens culinaris lectin (LCA)-fluorescein isothiocyanate (Seikagaku Corp.) on ice for 30 min. After washing with ice-cold PBS(−) twice, the cells were resuspended in 500 μl of PBS(−). A flow cytometric analysis was performed using a FACScan instrument (BD Biosciences) operating with CELLquest software.

**EGF Binding Assay**—The cells were seeded at a density of 1 × 10⁵ cell/well in 24-well plates and incubated overnight. The medium was then replaced with Dulbecco’s modified Eagle’s medium, which contained 0.1% BSA (M-BSA), and incubated for 20 min at 37 °C. After replacing the medium with ice-cold M-BSA, EGF mixture was added, followed by incubation for 2 h at 4 °C, as described previously (32). The cells were then washed with ice-cold PBS and hydrolyzed on 0.5 ml of 1 M NaOH. The radioactivity was counted with a γ counter.

**RESULTS**

The major phenotypes of Fut8 knock-out mice are: (i) early death during postnatal development (about 70% Fut8-null mice), (ii) epithysenike-like changes in the lung, and (iii) growth retardation. We have been attempting to clarify the underlying mechanisms for these phenotypes and found that down-regulation of TGF-β receptor is closely related with the epithysenike-like changes (28). To better understand the molecular mechanism of induction of retardation in Fut8−/− mice, we have established embryonic fibroblast at 18.5 post-coitus from Fut8+/+ and Fut8−/− mice (28).

**Loss of Core Fucosylation in Fut8−/− Cells Is Rescued by Re-introduction of Fut8 Gene**—To clarify whether the loss of function of core fucosylation can be restored, the Fut8 gene was re-introduced into Fut8−/− cells immortalized by the introduction of a zeocine resistant vector (pcDNA3.1) containing the SV40 large T gene. As expected, Fut8 activities could not be detected in Fut8−/− cells, even with a six times longer incubation as that used for Fut8+/+ cells (Fig. 2 and data not shown). Re-introduction of Fut8 gene into Fut8−/− cells resulted in recovery of Fut8 activities, the levels of which were comparable with those in Fut8+/+ cells.

On the other hand, the reaction products of Fut8, core fucosylated N-glycans were analyzed by means of the AAL lectin, which preferentially recognizes the core fucose in these cells. Under reducing conditions, several bands migrating at around 80–220 kDa in molecular mass were strongly stained with AAL in Fut8+/+ cells but only faintly stained in Fut8−/− cells (Fig. 3A). The reactive staining lost in Fut8−/− cells was completely rescued by restoring the Fut8 gene to Fut8−/− cells, suggesting that the post-translational modification by core fucosylation on N-glycans is only catalyzed by the Fut8 gene.

Furthermore, the expression levels of core fucosylation on the cell surface were examined by a FACS analysis using the LCA, which recog-
Fut8 Is Needed for the Function of EGFR

izes the α1,6-fucosylated trimannosyl core structures of N-linked oligosaccharides. The binding ability of the LCA lectin was significantly decreased in Fut8−/− cells, compared with Fut8+/+ cells and the cells in which the Fut8 gene had been restored (Fig. 3C).

Tyrosine Phosphorylation Level of EGFR Was Decreased in Fut8−/− Mice and Cells—EGF is a major multifunctional mitogen, which plays important roles in cell growth, cell differentiation, and cell migration. Several studies have shown that the remodeling of N-glycans on EGFR can modulate EGF-mediated intracellular signaling. Therefore, the issue of whether core fucosylation is required for the biological functions of EGFR was investigated. As shown in Fig. 4A, core fucosylation was expressed on EGFR in Fut8−/− cells but abolished on EGFR from Fut8+/+ cells. The re-introduction of the Fut8 gene restored the core fucosylation that was lost in Fut8−/− cells. No significant differences in the expression levels of EGFR on cell surface were found as confirmed by biotin labeling between the cells (Fig. 4B). The binding of EGF to the extracellular domain of the EGFR induces the activation of its intrinsic tyrosine kinase activity, leading to the phosphorylation of receptor tyrosine residues (18, 19). The phosphorylation levels of EGFR stimulated with EGF were increased in a dose-dependent manner in Fut8−/− cells. Interestingly, the stimulation was significantly suppressed in Fut8−/− cells, whereas the responsiveness was rescued in the restored cells (Fig. 4C). The cellular tyrosine phosphorylation levels are regulated by tyrosine kinases and tyrosine phosphatases. To determine whether or not tyrosine phosphatases affect the levels of phosphorylation of EGFR, we performed an In-blot phosphatase assay in vitro and found that there are no significant changes in the total activities of tyrosine phosphatase for phosphorylated EGFR between Fut8-null and wild-type cells (Fig. 4E). Moreover, we found that tyrosine-phosphorylated levels of EGFR in Fut8-null embryos were lower than that in wild-type embryos (Fig. 4F). Taken together, these results strongly suggest that the core fucosylation of EGFR can modulate its biological functions.

Down-regulation of Phosphorylated JNK and ERK in Fut8−/− Cells—It is well established that EGF activates the Ras/MAP kinase cascade to control cell growth. To determine whether core fucosylation is also important for EGF-mediated intracellular signaling, downstream signaling molecules such as JNK and ERK1/2 were examined by immunoblotting with anti-phospho-JNK and ERK antibodies. JNK and ERK phosphorylation levels, as induced by EGF, were greatly enhanced in Fut8+/+ cells, whereas marginal activation of JNK or ERK was detected in Fut8−/− cells after 5 min of incubation with EGF (Fig. 5, A and B). Consistent with the phosphorylation levels of EGFR as described in Fig. 5, the down-regulation of JNK and ERK activation in Fut8−/− cells was much more obvious at low concentrations of EGF stimulation (~0.05 ng/ml) rather than higher concentrations (0.1~ ng/ml), indicating the high binding affinity of EGF to its receptor is mainly down-regulated by a lack of core fucosylation. In fact, it has been reported that EGFR kinase activation occurs exclusively through the high affinity subclass (33). It is noteworthy that down-regulation of phosphorylation of ERK induced by PDGF was also observed in Fut8−/− cells (Fig. 5C). Although we did not find significant changes in fibroblast growth factor-mediated signaling (Fig. 5D), the possibility that other growth factor receptor-mediated signaling may also affect cell growth cannot be excluded.

Core Fucosylation Affects High Affinity Binding of EGF to EGFR—To elucidate the mechanism by which core fucosylation affects the EGF signaling, a binding analysis of 125I-EGF to EGFR in three types of cells was performed (Fig. 6). As shown in Fig. 6A, the binding of 125I-EGF to EGFR was reduced in Fut8−/− cells compared with Fut8+/+ or the restored cells at low doses, whereas similar levels of binding were found at relatively high concentrations. A Scatchard analysis revealed that both low and high affinity binding of EGFR were present in Fut8+/+ (Kd values are 269 and 1052 pm for low and high affinity, respectively) and the restored cells (Kd values are 253 1079 pm for low and high affinity,
FIGURE 4. Tyrosine phosphorylation levels of EGFR upon EGF stimulation. A, lectin blot analysis of the immunoprecipitated EGFR from Fut8+/−, Fut8−/−, and restored cells. EGFR was immunoprecipitated from whole cell lysate with anti-EGFR antibody and subjected to 7.5% SDS-PAGE. The blots were probed by AAL (upper panel) and reprobed with anti-EGFR antibody (lower panel). Re1, clone 1 restored cell; Re2, clone 2 restored cell; WB, Western blot. B, cell surface biotinylation and immunoprecipitation of EGFR from Fut8+/−, Fut8−/−, and restored cells. Cells were biotinylated, and whole lysates were immunoprecipitated with anti-EGFR antibody. The samples were subjected to 10% SDS-PAGE. C, after serum starvation overnight, cells were treated with EGF at the indicated concentrations for 5 min and then solubilized in lysis buffer as described under “Experimental Procedures.” Whole cell lysates were immunoprecipitated with the anti-EGFR. They were subjected to 7.5% SDS-PAGE, and then the blots were probed with anti-phosphotyrosine antibody. Re1, clone 1 restored cell; Re2, clone 2 restored cell; WB, Western blot. C, cell surface biotinylation and immunoprecipitation of EGFR from Fut8+/−, Fut8−/−, and restored cells. Cells were biotinylated, and whole lysates were immunoprecipitated with anti-EGFR antibody. The samples were subjected to 10% SDS-PAGE. C, after serum starvation overnight, cells were treated with EGF at the indicated concentrations for 5 min and then solubilized in lysis buffer as described under “Experimental Procedures.” Whole cell lysates were immunoprecipitated with the anti-EGFR. They were subjected to 7.5% SDS-PAGE, and the blots were probed with anti-phosphotyrosine (pTyr, upper panel) and anti-EGFR antibody (lower panel). D, quantification of phosphotyrosine levels of EGFR from three separate experiments was analyzed by NIH Image 1.63. Each bar represents the mean ± S.D. E, in-blot phosphatase assay. The each membrane slice was incubated with or without 0.5 ml of Fut8+/− or Fut8−/− cell lysates at the indicated concentrations for 30 min at 1 °C. Phosphorylated EGFR was detected with anti-phosphotyrosine antibody. (−), incubated with lysis buffer only. F, whole 18.5-day embryos were homogenized in lysis buffer. The supernatant (~3 mg) was pre cleared by 30 μl of protein G-Sepharose (50% slurry) and then immunoprecipitated with anti-EGFR antibody. Phosphorylated EGFR was detected with anti-phosphotyrosine. IP, immunoprecipitation.

FIGURE 5. Down-regulation of phosphorylated JNK and ERK in Fut8−/− cells. These serum-starved cells of Fut 8+/+, Fut8−/−, or the restored cells were treated with EGF (A, B), PDGF (C), and fibroblast growth factor (FGF) (D) at the indicated concentrations for 5 min and solubilized in lysis buffer as described under “Experimental Procedures.” Whole cell lysates were subjected to 10% SDS-PAGE. The blots were probed with anti-phospho-JNK (A, upper), anti-JNK1 (A, lower), anti-phospho-ERK1/2 (B–D, upper), and anti-ERK1/2 (B–D, lower).

respectively, but only low affinity EGFR was detected in Fut8−/− cells (Kd = 1233 pM) (Fig. 6B). Thus these results suggest that the modulation of N-glycans by core fucosylation on EGFR may regulate the high affinity binding EGF to EGFR, which is required and sufficient for EGF-induced responses (34–36) but not for the low affinity of EGFR.

**DISCUSSION**

Certain N-glycan structures of a number of glycoproteins, particularly growth factor receptors and adhesion molecules, appear to contribute to the folding, stability, and biological function of the molecules. In the present study, the effects of Fut8 expression and its product, core fucosylation, on EGF signaling in Fut8−/−, Fut8−/−, and the re-introduction of Fut8 gene to Fut8−/− cells was investigated. We found that the EGF-induced phosphorylation of EGFR was down-regulated in Fut8−/− cells, compared with Fut8+/+ cells. Consistent with this observation, EGFR-mediated downstream signaling such as the phosphorylation of JNK or ERK was also decreased in Fut8−/− cells. These inhibitory effects in Fut8−/− cells were completely rescued by re-introduction of the Fut8 gene to Fut8−/− cells. Furthermore, the levels of phosphorylation of EGFR were reduced in knock-out mice, compared with wild-type mice. Our results provide clear evidence, for the first time, that core fucosylation may play an important role in EGFR-mediated biological functions.

Although several lines of evidence indicate that the oligosaccharide portion of the EGFR is important for its function, the effects of oligosaccharide may vary between cells lines. For example, U373 MG cells overexpressing GnT-III exhibit an inhibition of EGF binding to the cell surface and EGFR autophosphorylation (25). Consistent with this, the overexpression of GnT-III in PC12 cells down-regulates the binding of
EGF to EGFR, EGF autophosphorylation, and receptor-mediated ERK activation, resulting in the suppression of neuropeptide outgrowth (26). In those experiments, the alteration of N-glycans did not contribute to the expression levels of EGFR on cell surface. Recently it was also reported that N-glycans of EGFR as well as other cytokine receptors modified by GnT-V, which catalyzes the formation of GlcNAcβ1,6 branches, play an important role in the endocytosis of EGFR to regulate its expression levels on cell surface (37). Collectively, these results suggest that N-glycan is an important regulator in receptor-mediated signaling.

To our knowledge, no reports showing that core fucosylation regulates EGFR functions have appeared to date. In fact, N-glycans of EGFR purified from A431 cells have been characterized and found to contain a large population of core fucosylated N-glycans (38). On the other hand, the core fucosylated glycoprotein levels can be greatly up-regulated through the enhanced expression of Fut8 and/or FX, which is responsible for GDP-fucose synthesis, in human hepatocellular carcinoma (39), but the biological functions for the accumulation of core fucosylated proteins in HCC are unclear. EGFR represents a plausible candidate, since it plays crucial roles in cell growth, differentiation, and migration. The loss of functions in the responsiveness of EGFR to EGF stimulation in Fut8−/− cells could be completely rescued by re-introduction of the Fut8 gene. In addition, core fucosylation does not affect EGFR expression on the cell surface, indicating that core fucosylation may affect some conformational changes in EGFR. This notion is supported by evidence showing the binding affinity of EGFR to its receptor is down-regulated in Fut8−/− cells, compared with that in Fut8+/+ or restored cells.

It has been reported that the binding of EGF to EGFR exists in high affinity and low affinity classes (34, 35). Thus, the issue of whether no significant changes in EGFR-mediated signaling between those cells when treated with higher concentrations of EGF was addressed (Fig. 5, A and B, and data not shown). Consistent with this, a Scatchard analysis revealed that both high and low affinity binding of EGFR were present in Fut8−/− and restored cells. However, only low affinity binding of EGFR was detected in Fut8−/− cells (Fig. 6B). Therefore the possible reason for this can be explained by the fact that core fucosylation mainly regulates the high affinity binding of EGFR, which is required and sufficient for EGF-induced responses (33, 36). The precise reason for the regulation remains to be elucidated. It is reasonable to postulate that core fucosylation may also affect the biological functions of other growth factors and adhesion molecular receptors such as integrins, which control cell adhesion and cell migration. Actually, we also found that PDGF-mediated signaling was also down-regulated in Fut8−/− cells (Fig. 5C). We previously found that overexpression of Fut8 resulted in the accumulation of cholesterol esters in liver and kidney (40) and down-regulation of cell adhesion and migration in hepatoma cells (41).

In conclusion, we demonstrated some aspects of the biological significance of the core fucosylation on EGFR and EGFR-mediated intracellular signaling. The present study further supports the notion that N-glycans decorate glycoproteins on cell surface, where the N-glycans can have critical functions, and provides insight into the molecular mechanisms of core fucosylation-regulated cell growth and cell differentiation in Fut8−/− mice.

REFERENCES

Fut8 Is Needed for the Function of EGFR

Natl. Acad. Sci. U. S. A. 102, 15791–15796
Core Fucosylation Regulates Epidermal Growth Factor Receptor-mediated Intracellular Signaling
Xiangchun Wang, Jianguo Gu, Hideyuki Ihara, Eiji Miyoshi, Koichi Honke and Naoyuki Taniguchi

doi: 10.1074/jbc.M510893200 originally published online November 29, 2005

Access the most updated version of this article at doi: 10.1074/jbc.M510893200

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 41 references, 27 of which can be accessed free at http://www.jbc.org/content/281/5/2572.full.html#ref-list-1