Differential Terminal Fucosylation of N-Linked Glycans Versus Protein O-Fucosylation in Leukocyte Adhesion Deficiency Type II (CDG IIc)*

Laura Sturlia, Raajit Rampalb, Robert S. Haltiwangerc, Floriana Frusciones, Amos Etzionid, and Michela Tonetti**

From the aGianginna Gaslini Institute, 16147 Genova, Italy, the bDepartment of Biochemistry and Cell Biology, Institute for Cell and Developmental Biology, State University of New York at Stony Brook, New York 11794-5215, cDepartment of Experimental Medicine, University of Genova and Center of Excellence for Biomedical Research, 16123 Genova, Italy, and the dDepartment of Pediatrics, Meyer Children Hospital, Rambam Medical Center and B. Rappaport School of Medicine, Technion, 31096 Haifa, Israel

LAD II/CDG IIc is a rare autosomal recessive disease characterized by a decreased expression of fucosylated antigens on cell surfaces that results in leukocyte adhesion deficiency and severe neurological and developmental abnormalities. Its molecular basis has been identified as a defect in the transporter of GDP-L-fucose into the Golgi lumen, which reduces the availability of the substrate for fucosyltransferases. During metabolic radiolabeling experiments using [3H]fucose, LAD II fibroblasts incorporated significantly less radiolabel compared with control cells. However, fractionation and analysis of the different classes of glycans indicated that the decrease in [3H]fucose incorporation is not generalized and is mainly confined to terminal fucosylation of N-linked oligosaccharides. In contrast, the total levels of protein O-fucosylation, including that observed in Notch protein, were unaffected. This finding demonstrates that the decrease in GDP-L-fucose levels in the fibroblast Golgi caused by the LAD II defect does not impair bulk protein O-fucosylation, but severely affects the bulk addition of fucose as a terminal modification of N-linked glycans. These data suggest that the severe clinical abnormalities including neurological and developmental ones observed in at least some of the LAD II patients may be related to alteration in recognition systems involving terminal fucose modifications of N-glycans and not be due to a defective O-fucosylation of proteins such as Notch.

Fucosylated structures expressed on cell surfaces or secreted in biological fluids are involved in a variety of functions related to cell-to-cell adhesion and recognition processes. Alterations in the production of fucosylated glycoconjugates have been observed in development and differentiation, and in pathological conditions as well, including inflammation and tumor progression (1–5). Disruption of the FX gene, which codes for a key enzyme in fucose metabolism, results in mice that require fucose in their diet for survival, demonstrating the essential nature of fucosylation (6).

Fucose is present in both N-linked and mucin-type O-linked glycoproteins, where it is linked to the oligosaccharide chains as a terminal modification that is not further elongated (7). Recently, a new class of fucose-containing glycoproteins has been identified in which fucose is directly O-linked to a serine/threonine residue (8–9). O-fucose modifications have been reported to occur in two distinct sequence contexts: epidermal growth factor-like (EGF)1 repeats (8) and thrombospondin type 1 repeats (TSR) (10). Serum proteins, involved in blood clotting or clot dissolution, such as human factor VII, factor XII, uPA (urokinase-type plasminogen activator) and PA (tissue type plasminogen activator), are modified by O-fucose as a simple monosaccharide at a specific consensus sequence within their EGF repeats (11–16). Elongation of the O-fucose monosaccharide on EGF repeats to a tetrasaccharide can occur in a proteinspecific manner (e.g. factor IX, Notch and Notch ligands, Refs. 17–19). Elongation of O-fucose is initiated by Fringe, an O-fucose-specific β1,3-N-acetylgalactosaminyltransferase. Subsequent action of galactosyl- and sialyltransferases results in the formation of the final tetrasaccharide (Siaα2,3Galβ1,4GlcNAcβ1,3-Fucα1-O/S/T) (20–21).

Many reports have demonstrated an essential functional role for the O-fucose modification on proteins such as Notch, Crypo/Nodal, and uPA (Ref. 15 and 22–23; for recent reviews, see Refs. 24 and 25). The Notch receptor plays an essential role in numerous stages of development (26), and recent work has demonstrated that O-fucose is essential for Notch signaling. Reduction or elimination of the enzyme responsible for addition of O-fucose to proteins, protein O-fucosyltransferase 1 (O-FucT-1), causes strong Notch-like phenotypes in both Drosophila (27) and mice (28). In addition, the presence of an O-fucose glycan is essential in the Notch receptor system for the Fringe-mediated modulation of Notch activation in vivo in both Drosophila and mammalian cells (20–21). The fact that a defect in O-fucosylation of Notch results in embryonic lethality in mice raised the question of whether Notch is properly O-fucosylated in LAD II/CDGS IIc patients.

Recent work by Hofsteenge and co-workers (10, 29) has demonstrated that several extracellular matrix glycoproteins, in-
including thombopondin-1, F-spondin and properdin, are modified with O-fucose at a consensus site within TSRs. In contrast to EGFR repeats, the O-fucose on TSRs exists as either the monosaccharide Fuc-O-Ser/Thr or the disaccharide Glc-Fuc-O-Ser/Thr. A similar modification (Glc-β1,3Fuc) has also been observed in CHO cells, where it represents a quite abundant form of glycosylation (30). Although the function of the O-fucose on TSRs is not yet known, it occurs in a predicted cell interaction domain, suggesting that the modification may play a role in regulating cellular interactions with the extracellular matrix (31).

The importance of fucose in modulating glycan functions is well demonstrated by the human genetic disease LAD II/CDGS Ic, which is characterized by the absent or reduced expression of fucosylated glycoconjugates on cell surfaces, including blood group H and Lewis antigens (32). Patients affected by this syndrome present with severe mental and growth retardation, facial and skeletal abnormalities and immunodeficiency characterized by recurrent bacterial infections. This latter finding has been related to a reduced leukocyte rolling on endothelial cells mediated by the selectins, which are unable to recognize their oligosaccharide ligands, impairing leukocyte recruitment into the inflamed tissues. Conversely, the specific causes that lead to the severe neurological, developmental, and morphologic defects need still to be clarified. The molecular basis of LAD II/CDGS Ic syndrome has been found in a defect in GDP-β-fucose import into the Golgi system (33–36). The decreased GDP-β-fucose availability for the fucosyltransferases within the Golgi lumen explains the lower fucose content in glycoconjugates. However, the fact that some fucosylated antigens are undetectable (i.e. H antigen, selectin ligands), while LAD II cells incorporate low, but detectable levels of fucose into macromolecules, suggested that not all fucose-containing glycoconjugates are comparably decreased (36). The aim of the present study was the characterization of the residual fucose-containing glycoconjugates in cultured fibroblasts from a LAD II patient of Arab origin, in order to determine how the decreased availability of GDP-β-fucose inside the Golgi can affect their type and composition. Both terminal fucosylation of N-linked glycans and protein O-fucosylation are clearly involved in development and differentiation processes. Identification of the class of glycans that is most heavily affected in LAD II patients should provide clues to the role of these forms of fucosylation in the severe developmental defects observed in these patients.

EXPERIMENTAL PROCEDURES

Cell Lines and Metabolic Labeling—Fibroblasts of one LAD II patient of Middle Eastern origin (35) and of two unrelated, age-matched controls were derived from dermal biopsies, using standard procedures. Informed consent for the study was obtained from patient and control parents. Cells were maintained in RPMI 1640/10% fetal calf serum/2 mM glutamine (Invitrogen). No differences in morphology, adhesion, and growth kinetic were observed between patient and control cells. For experimentation, cells were seeded in 25 cm² flasks (BD Biosciences, Rockland, MA) and were incubated for 72 h in the presence of 50 μM [3H]fucose (PerkinElmer Life Sciences, Milan, Italy; 3.2 TBq/mmol; final specific activity 7.5 MBq/mmol). Incubation with [3H]fucose was repeated at 24-h intervals to maintain the maximum specific activity of [3H]fucose as described above. [3H]Fucose (0.5 μM/ml from Sigma) was added together with the radiolabeled fucose. No toxicity, determined by MTT (3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay, was observed in these incubation conditions. Incorporation of the radiolabel in macromolecules was determined after PFA (phospohtungic acid/HCl pre-
Notch1 presence in fibroblasts lysates before and after immunoprecipitation was analyzed by Western blotting experiments using Na antibody. The lysates were subjected to SDS-PAGE analysis on a 7.5% gel and, after separation, the proteins were transferred onto a PVDF membrane. Detection was performed with the ECL Plus detection system (Amersham Biosciences) according to the manufacturer's instructions.

RESULTS

LAD II Fibroblasts Incorporate Significantly Less \(^{3}\text{H}\text{fucose}\) into N-Glycans than Control Fibroblasts—To initially assess the consequences of a reduced uptake of GDP-L-fucose into the Golgi apparatus on fucosylated glycan composition in fibroblasts, cells were metabolically labeled with 50 \(\mu\text{M}\) \(^{3}\text{H}\text{fucose}\). As expected, uptake of \(^{3}\text{H}\text{fucose}\) was significantly reduced in LAD II samples compared with controls (Fig. 1A). Tunicamycin treatment was able to reduce \(^{3}\text{H}\text{fucose}\) incorporation in macromolecules. However, this tunicamycin-induced decrease of label uptake in glycoproteins was not comparable between the two samples, the LAD II cells being less affected than controls (Fig. 1A). No differences between LAD II and control cells were observed after labeling with \(^{3}\text{H}\text{glucosamine}\), either alone or in the presence of tunicamycin (Fig. 1B). These data suggested as a first approximation that the decrease in fucose incorporation in LAD II cells is not equally distributed in all glycan classes, but involves mainly the N-linked oligosaccharides, and it is not accompanied by a general alteration in glycoconjugate composition.

To test this hypothesis, cells were incubated in the presence of \(^{3}\text{H}\text{fucose}\) and subjected to fractionation, in order to isolate and analyze N- and O-linked glycans. Aliquots of the recovered total glycoproteins were then used to determine radioactivity incorporated in glycoproteins (Fig. 2A) or subjected to hydrolysis followed by HPAEC-PAD analysis to determine total amount of bound fucose (Fig. 2B) and fucose-specific activity (Fig. 2C). As already observed for tunicamycin experiments, total radioactivity and the amount of fucose incorporated in macromolecules were decreased in LAD II samples (Fig. 2, A and B). \(^{3}\text{H}\text{fucose}\) final specific activity, determined by HPAEC-PAD analysis after acid hydrolysis of total glycoproteins, was slightly different between control and LAD II (Fig. 2C), possibly due to a different contribution of the salvage pathway to the cytosolic GDP-L-fucose pool in the two samples. The specific activity of \(^{3}\text{H}\text{fucose}\) on total glycoproteins was then used to estimate the picomoles of total fucose bound to glycoproteins and in the different glycan fractions.

The profiles of elution from G-50 column of \(^{3}\text{H}\text{fucose}\)-labeled total glycoproteins after PNGase F treatment to release N-linked oligosaccharides are reported in Fig. 3A. Radioactivity eluting in correspondence to the oligosaccharide peak was highly decreased in LAD II samples, while the PNGase-resistant fraction was comparable between LAD II and controls (Fig. 3A). No differences in the elution profile were observed between LAD II and controls when \(^{3}\text{H}\text{glucosamine}\) was used as label (Fig. 3B). This strongly suggests that the reduction observed is specific for fucose, and it is not accompanied by significant differences in N-glycan composition. Fucose content, estimated using \(^{3}\text{H}\text{fucose}\)-specific activity in the pooled fractions containing the N-linked oligosaccharides, was markedly reduced in LAD II cells, while the amount of protein-bound, PNGase-resistant fucose was less affected in patient samples (Fig. 3C). This finding was in accord with the previous data obtained with tunicamycin.

LAD II and Control Fibroblasts Contain Similar Levels of O-Fucose Saccharides—Labeled proteins recovered from G-50 column were then subjected to alkali-induced \(\beta\)-elimination in the presence of NaBH\(_4\) in order to release O-linked oligosaccharides and, possibly, residual PNGase F-resistant N-linked
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To characterize the size and composition of the third peak, which is hypothesized to contain O-fucosylated species, the corresponding fractions were pooled and subjected to gel filtration analysis on a Superdex column. The profile of elution was comparable between controls and LAD II and showed two species, corresponding to disaccharides and to monosaccharides, respectively (Fig. 5, A and B). HPAEC analysis of the monosaccharide indicated the presence of fucitol, which is formed when O-fucosylated monosaccharide is released by β-elimination followed by NaBH₄ reduction of the aldehyde group (not shown). HPAEC profiles from the fractions containing the disaccharide correspond to the elution peaks of maltopentaose (MP) and fucose (F). Radioactive recovery after G-50 column chromatography was between 70 and 80% for all samples. C, fractions from the three peaks identified from G-50 analysis corresponding to the β-elimination-resistant material, high/medium molecular weight oligosaccharides, and small oligosaccharides/monosaccharides were pooled together. The amount of fucose was estimated using [3H]fucose-specific activity.

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**Fig. 3.** Elution profiles from Sephadex G-50 column obtained after treatment of total glycoproteins with PNGase F. A, total glycoproteins obtained from metabolic labeling of fibroblasts with 50 μm [3H]fucose. B, total glycoproteins obtained after treatment with [3H]glucosamine. Control, ■; LAD II, ○. 6 mg of total glycoproteins were treated for each sample. Fractions (1.0 ml) were collected at 1-min intervals starting 10 min after the beginning of elution, and 50 μl were used for scintillation counting. Total radioactivity recovery after chromatography ranged between 90 and 95% for each sample. PNGase-resistant glycoproteins eluted from fractions 5–10. N-linked oligosaccharides eluted from fractions 11–28. Elution volume of glycoproteins was determined using a parallel sample in the absence of PNGase F treatment. C, fractions obtained from G-50 chromatography after PNGase treatment of total glycoproteins were pooled together to obtain PNGase-resistant proteins and N-linked oligosaccharides. Fucose amount was estimated from incorporated radioactivity in each pool, using [3H]fucose-specific activity.

**Fig. 4.** Elution profiles from Sephadex G-50 column obtained after β-elimination of PNGase-resistant glycoproteins. A, PNGase-resistant glycoproteins obtained from metabolic labeling of fibroblasts with 50 μm [3H]fucose. B, PNGase-resistant glycoproteins obtained after incubation with [3H]glucosamine. Control, ■; LAD II, ○. PNGase-resistant glycoproteins derived from the initial enzymatic treatment of 6 mg of protein for each sample. Fractions (1.0 ml) were collected at 1-min intervals starting 10 min after the beginning of elution, and 100 μl were used for scintillation counting. Three main peaks were identified: fractions 5–10, β-elimination-resistant material; fractions 11–23, high/medium molecular weight oligosaccharides; fractions 24–35, small oligosaccharides/monosaccharides. Arrows correspond to the elution peaks of maltopentaose (MP) and fucose (F). Radioactive recovery after G-50 column chromatography was between 70 and 80% for all samples. C, fractions from the three peaks identified from G-50 analysis corresponding to the β-elimination-resistant material, high/medium molecular weight oligosaccharides, and small oligosaccharides/monosaccharides were pooled together. The amount of fucose was estimated using [3H]fucose-specific activity.
noreactive bands disappeared, confirming that all Notch protein was immunoprecipitated (Fig. 6A).

The immunoprecipitated proteins, either untreated or treated with PNGase F to eliminate N-linked oligosaccharides, were separated by SDS-PAGE and analyzed by autoradiography (Fig. 6B). Before PNGase F, bands of ~200 kDa, which correspond to the molecular weight of the extracellular domain of Notch1 (42), were observed both in controls and LAD II samples. The amount of radioactivity detected in these bands reflected [3H]fucose incorporation both as terminal modification of N-linked glycans and as O-fucosylation and, as expected, was severely decreased in LAD II cells, confirming the defective incorporation in N-linked oligosaccharides. After PNGase F treatment, together with a detectable shift in molecular mass due to removal of N-linked oligosaccharides (18), comparable levels of PNGase F-resistant radioactivity (corresponding to O-fucosylated species in Notch protein) were observed in both controls and LAD II cells. Very similar results were obtained after labeling of the cells with [14C]fucose and scintillation counting of the gel slices following immunoprecipitation and SDS-PAGE separation of the bands (not shown). These results demonstrate that, while [3H]fucose incorporation as terminal fucosylation of N-linked glycans is severely affected, the O-fucosylation on EGF repeats on Notch1 protein is not significantly reduced in LAD II fibroblasts. The same conclusion holds for total O-fucosylation.

DISCUSSION

LAD II/CDGS IIc syndrome is characterized by a defective GDP-L-fucose import into the Golgi system, due to point mutations in the specific transporter (34–35). The decreased availability inside the Golgi of the substrate for fucosyltransferases causes the generalized defect in fucose expression on glycoconjugates. However, it is not presently clear if all glycan species are equally involved, or, due to the different characteristics of the fucosyltransferases, some species are more affected than others. The data obtained from this study indicate that in fibroblasts the decrease in fucose expression affects mainly N-linked oligosaccharides, where fucose represents a terminal modification that is not further elongated. Conversely, the total amounts of O-fucose monosaccharide and of the disaccharide Glc-β1,3-Fuc-O(S/T) are even slightly increased in LAD II samples compared with controls. These results indicate that total levels of O-fucosylation are not affected by a reduced availability of GDP-L-fucose inside the Golgi apparatus of LAD II fibroblasts.
O-fucosylation has been described so far in both EGF-like repeats and TSRs, and at least two different protein O-fucosyltransferases are responsible for modification of these repeats. O-Fuc-T-1, which modifies EGF repeats, has been cloned and characterized (43–44); conversely, nothing is as yet known about the enzyme(s) responsible for fucosylation of TSRs. However, preliminary observations suggest that O-Fuc-T-1 will not modify TSRs and that a separate enzymatic activity exists. Since total levels of the disaccharide Glc-β3,4-Fuc-α1,3/S(T), which is characteristic of TSRs (10, 29), are normal in LAD II cells, it can be assumed that O-fucosylation of this type of repeats is in general not affected. Conversely, we were consistently unable to identify by chromatographic methods O-fucose elongated to the tetrasaccharide form, which, together with O-fucose monosaccharide, is a typical of modification of EGF-like repeats of proteins such as Notch. However, the amount of [3H]fucose-labeled tetrasaccharide bound to Notch can be expected to be very low and below the detection limits by chromatographic methods. The data obtained after immunoprecipitation of [3H]fucose-labeled Notch1 confirmed a significant reduction in the incorporation of this sugar in N-linked glycans, while comparable amounts between LAD II and control cells were observed after PNGase treatment of immunoprecipitated Notch proteins. This indicates that O-fucosylation of EGF-like repeats is also not affected in LAD II fibroblasts.

A potential explanation for the difference between addition of terminal fucose and O-fucosylation could rely in a different affinity for GDP-β-fucose, the protein fucosyltransferases having a lower $K_m$ for the nucleotide-sugar compared with the other fucosyltransferases that add fucose as terminal modification of the oligosaccharide chains. For instance, O-Fuc-T-1, which modify EGF repeats, has a $K_m$ for GDP-β-fucose of ~5 $\mu$m, while several fucosyltransferases involved in terminal fucosylation of N-glycans have nearly 10-fold higher $K_m$ values (43–44). A similar phenomenon has been described in a mutant line of MDCK cells, which is severely defective for UDP-galactose transport into the lumen of Golgi vesicles (45). In these cells, galactosylation of keratan sulfate as well as of glycoproteins and glycolipids is highly decreased, while that of heparan sulfate and chondroitin 4-sulfate is unaffected. This suggested that the $K_m$ for UDP-galactose of the galactosyltransferases involved in the biosynthesis of the linkage region of proteoglycans is significantly lower than that of the other galactosyltransferases and that UDP-galactose availability may be able to modulate proteoglycan expression (45).

Another possible explanation for the normal levels of O-fucosylation in LAD II could derive from a different localization of the transferases. It is in fact known that terminal fucosylation of N-glycans is a late event in the formation of the protein-bound oligosaccharides and the fucosyltransferases responsible for this fucose transfer are mainly localized in trans-Golgi and trans-Golgi network. Conversely, the subcellular site of protein O-fucosylation is not yet clear. The membrane-bound localization of the protein O-fucosyltransferase identified so far and the presence of mostly high mannose type oligosaccharides on it suggest that this protein is probably localized in either the endoplasmic reticulum or the cis-Golgi region (43). Other than localization of GDP-β-fucose transport activity to the Golgi apparatus (46), no information is presently available on the distribution of the GDP-β-fucose transporter within the Golgi system. It is not known if transport occurs through only one protein species or other isoforms that can be expressed at different Golgi sites.

Since data were obtained in fibroblasts from a LAD II patient with a specific point mutation in the GDP-β-fucose transporter, it cannot be excluded that in other tissues or in patients bearing other mutations different fucosylation patterns can occur. However, the extensive decrease of fucose as terminal modification of N-linked glycans observed in our study is in agreement with an almost absent expression of blood group H antigen and of Lewis ligands for the selectins in blood cells (32). Thus, the severe impairment of growth and development affecting these LAD II patients may be related to a generalized defect of selectin/ligand interaction or of other mechanisms involving recognition of fucose as terminal modification, rather than to a bulk defect in O-fucosylation. Further studies are required to understand if a limited GDP-β-fucose supply is also able to differentially affect the activity of the several α1,2, α1,3/4, and α1,6 fucosyltransferases and if specific types of terminal fucose linkages are more affected than other ones in N-glycans from LAD II fibroblasts. For instance, genetic ablation of FUT8 (responsible for addition of α1,6-linked fucose to the N-linked core GlcNAc) appears to be semi-lethal. Mice die a few weeks after birth and display LAD II-like characteristics, thus suggesting that core fucosylation is essential for proper development.

The mechanisms that underlie and control the production of fucosylated glycans are not yet completely understood. The results obtained in the present study give some insights into them, indicating that GDP-fucose transport into the Golgi lumen is able to regulate the biosynthesis of fucosylated glycoconjugates. The importance of understanding these processes derives from the fact that both the enzymes involved in the biosynthesis of GDP-β-fucose and the subsequent transport of this metabolite into the Golgi represent distinctive targets for the pharmacological modulation of the expression of fucose-containing structures (i.e. SLeX). This approach perhaps may be used in therapy in order to disrupt selectin-mediated intercellular adhesion processes (i.e. during inflammation, graft rejection, tumor metastasis). A possible drawback of such therapies could be represented by an impaired production of other classes of glycans, such as O-fucosylated glycoproteins, which could be essential for other cellular functions, thus causing unwanted side effects. Our results indicate that, by choosing the appropriate target for a pharmacological treatment, it would be possible to modulate selectively the expression of fucose as a terminal modification of N-linked glycans, leaving O-fucosylation unaffected.

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