Available online at www.sciencedirect.com
ScienceDirect
Biochemical and Biophysical Research Communications 358 (2007) 41–46
BBRC
www.elsevier.com/locate/ybbrc

β4GalT-II increases cisplatin-induced apoptosis in HeLa cells depending on its Golgi localization

Jianhai Jiang, Jin Zhou, Yuanyan Wei, Jialin Shen, Dan Liu, Xiaoning Chen, Si Zhang, Xiangfei Kong, Xiaojing Yun, Jianxin Gu *

Key Laboratory of Glycoconjuates Research, Ministry of Public Health & State Key Laboratory of Genetic Engineering and Gene Research Center, Shanghai Medical College of Fudan University, Shanghai 200032, People's Republic of China

Received 16 March 2007
Available online 18 April 2007

Abstract

β1,4-Galactosyltransferase II (β4GalT-II) is one of the enzymes transferring galactose to the terminal *N*-acetylglucosamine of complex-type *N*-glycans and its expression is significantly altered during oncogenesis with unknown functions. Here, we reported for the first time the pro-apoptotic role of β4GalT-II in tumor cells. The level of β4GalT-II mRNA expression was obviously decreased during HeLa cell apoptosis induced by cisplatin. Interestingly, the ectopic expression of β4GalT-II in HeLa cells markedly increased apoptosis and cleavage of PARP induced by cisplatin as well as the expression of pro-apoptotic protein Bax. Furthermore, deletion of Golgi localization domain abolished the apoptotic role of β4GalT-II in HeLa cells. Collectively, these results suggest that β4GalT-II increases HeLa cell apoptosis induced by cisplatin depending on its Golgi localization, which indicates that β4GalT-II might contribute to the therapeutic efficiency of cisplatin for cervix cancer.

Keywords: β4GalT-II; Apoptosis; Cisplatin; HeLa cells; Golgi localization

Apoptosis, which is a common cellular response to stress caused by environmental challenges [1], plays critical roles in cancer chemotherapy [2]. Cisplatin, a chemotherapeutic agent, is known to cause DNA damage by forming DNA–DNA or DNA–protein adducts that trigger cell apoptosis, and is widely used in the treatment of solid tumors, including ovarian, testicular, cervical, and small cell lung cancers [3,4]. Although cisplatin therapy is effective in treating solid tumors, the acquisition of resistance by tumor cells to cisplatin is one of the major problems in cisplatin with largely unknown mechanisms [5].

β1,4-Galactosyltransferase (GalT) family are the enzymes responsible for the biosynthesis of *N*-acetyllactosamine on *N*-glycans by transferring UDP-galactose to the terminal *N*-acetylglusamine (*N*-GlcNAc) residues and this family consist of seven members, from β4GalT-I to β4GalT-VII [6,7]. β4GalT-II, a member of β1,4-galactosyltransferase family, is a major regulator of the synthesis of glycans involved in neuronal development [8,9]. The expression change of *β4GalT-II* has been investigated using NIH3T3 and the highly malignant transformed cell line MTAg. Northern blot analysis revealed that the transcript of *β4GalT-II* gene decreased to one-fifth in the transformed cells [10]. In addition, our previous study showed that the expression of *β4GalT-II* was increased in the process of glioma development [11]. In spite of this knowledge, currently little is known about the role of β4GalT-II in tumor cells.

In this study, we investigated the contribution of β4GalT-II in cisplatin-induced apoptosis. The ectopic expression of β4GalT-II in HeLa cells markedly increased cisplatin-induced apoptosis and the expression of Bax and Bad. Moreover, deletion of Golgi apparatus location domain abolished the apoptotic role of β4GalT-II in HeLa

* Corresponding author. Fax: +86 21 64164489.
E-mail address: jxgu@shmu.edu.cn (J. Gu).

0006-291X/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbrc.2007.04.044

cells. Taken together, our results reveal that β4GalT-II increases HeLa cell apoptosis induced by cisplatin depending on its Golgi localization, which elicits survival signals in HeLa cells.

Experimental procedures

Materials. Restriction enzymes, bovine calf serum, DMEM medium, Trizol regent, and Lipofectamine reagent were purchased from Invitrogen. The anti-GFP antibody, Hechst33258, cisplatin, adriamycin and etoposide were purchased from Sigma Chemical. The anti-Bad, anti-Bid, anti-Bax, anti-Bak, anti-Bcl-2 and anti-PARP antibodies were purchased from Cell Signal. The anti-GAPDH antibody was purchased from Santa Cruz Biotechnology. The EGFPN3 vector has been previously described [12].

Cell culture and transfection. HeLa cells were cultured in Dulbecco's modified Eagle's medium. Cell transfection was performed with Lipofectamine (Invitrogen) according to the manufacturer's instructions.

Analysis of apoptosis by fluorescence staining and flow cytometry and Western blot analysis. Fluorescence staining and flow cytometry have been described previously [13]. Western blot was performed as previously described [14], using an antibody to GAPDH to ensure equivalent loading.

Plasmids. The entire open reading frame of human β4GalT-VII gene was obtained from HeLa cells total RNA by RT-PCR. Total RNAs were extracted from HeLa cells with Trizol reagent. Reverse transcription was performed according to the instructions included with the TaKaRa RNA PCR Kit. The primers used were β4GalT-VIIs (5′-TATCTCGAGATGTTCCCCTCGCGGAG-3′), β4GalT-VIIas (5′-TATGGATCCGCTGAATGTGCACCAGG-3′). Following digestion with restriction enzymes, the β4GalT-VII fragment was directionally cloned into *Xho*I/*Bam*HI digested EGFPN3 vector to generate a "full-length" β4GalT-VII. The entire open reading frame of human β4GalT-II gene was obtained using the same manner. The primers used were β4GalT-IIs (5′-TATCTCGAGATGAGCAGACTGCTGGGGGGGACG-3′), β4GalT-IIas (5′-TATGGATCCGCCCCGAGGGGGCCACGACGG-3′). Following digestion with restriction enzymes, the β4GalT-II fragment was directionally cloned into *Xho*I/*Bam*HI digested EGFPN3 vector to generate a "full-length" β4GalT-II (FL(1–372aa)). Expression vectors containing sequentially truncated fragments (N(1–32aa), C(15–327aa)) of β4GalT-II were prepared in a similar manner. The transmembrane domain deletion construct D(15–32aa) was created from β4GalT-II by PCR using TakaRa MutantBEST mutagenesis kit and the listed primers (forward 5′-GACGTCTACGCCCAGCACCTGGCCT-3′ and reverse 5′-CTTGCAGACGCGCTCCAGCGTCC-3′). The plasmid of GFP-tagged β4GalT-I has been described previously [12]. The expression plasmids for human β4GalT-III to β4GalT-VI were kindly provided by Prof. Kiyoshi Furukawa (Tokyo Metropolitan Institute of Gerontology, Japan). The plasmids of GFP-tagged β4GalT-III to β4GalT-VI were constructed in a similar manner.

Reverse transcription (RT)-PCR. Reverse transcription PCR were performed as previously described [12]. Primers used for PCR were as follows: β4GalT-IIs, 5′-CGGTCATCATCCCCTTTAGA-3′ and β4GalT-IIas 5′-ATTGGTGAAGAGTGGTTGCC-3′. The PCR product for β4GalT-II was 635 bp.

Results

The effect of DNA-damaging agents on β4GalT-II mRNA expression

To investigate the contribution of β4GalT-II in cell apoptosis, we first examined the expression of β4GalT-II in HeLa cells treated with cisplatin, etoposide or adriamycin, respectively, which are widely known to be used in the treatment of solid tumors and kill cells through the induction of apoptosis [15]. RT-PCR was performed to analyze the level of *β4GalT-II* mRNA expression in HeLa cells untreated or treated with cisplatin, etoposide or adriamycin in the indicated concentration. As depicted in Fig. 1, the mRNA expression of *β4GalT-II* was significantly decreased in response to cisplatin in a dose-dependent manner; however, compared to the controls, the mRNA expression of *β4GalT-II* was not significantly altered in response to etoposide or adriamycin.

Overexpression of β4GalT-II promotes cisplatin-induced apoptosis in HeLa cells

The effect of cisplatin on β4GalT-II mRNA expression motivated us to investigate the contribution of β4GalT-II in cisplatin-induced apoptosis. To address this point, EGFP-tagged β4GalT-II expression construct was constructed and transiently transfected into HeLa cells (Fig. 2A). And, we investigated the effect of β4GalT-II on apoptosis after cisplatin treatment for 24 h. As shown in Fig. 2B, the percentage of apoptotic cells in β4GalT-II-overexpressed HeLa cells was markedly increased, compared to that of the controls by FACS assay. This conclusion was further supported in Figs. 2C and D. β4GalT-II sensitized HeLa cells to cisplatin-induced apoptosis as indicated by fragmented and condensed nuclei, indicating the pro-apoptotic role of β4GalT-II in HeLa cells (Fig. 2C). In addition, β4GalT-II overexpression markedly increased the cleavage and expression of PARP (Fig. 2D), which is implicated in the apoptosis process in numerous cells induced by DNA-damaging agents [16,17]. To identify the proteins responsible for the enhanced apoptotic response in HeLa cells transiently transfected with β4GalT-II, we explored whether β4GalT-II influenced on the expression of Bcl-2 family members which play important roles in the apoptosis progress [18]. As shown in Fig. 2E, β4GalT-II overexpression increased the expression of Bax and Bad, without changing the expression of the other examined proteins. Taken together, overexpression of β4GalT-II contributed in cisplatin-induced apoptosis.

Ectopic expression of β4GalT-II increases cisplatin-induced apoptosis in HeLa cells depending on its Golgi localization

The EXPASY search program predicted that β4GalT-II protein consisted of a short NH2-terminal cytoplasmic

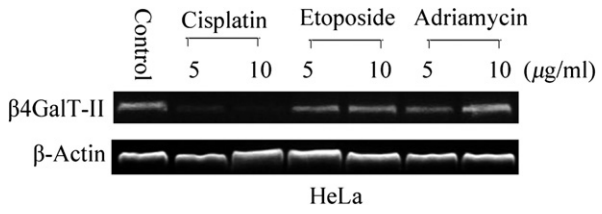

Fig. 1. The effect of DNA-damaging agents on β4GalT-II mRNA expression in HeLa cells. RT-PCR analysis of endogenous β4GalT-II mRNA expression level in HeLa cells untreated or treated with cisplatin, etoposide or adriamycin in the indicated concentration for 24 h. Level of β-actin mRNA expression was assessed as a loading control.

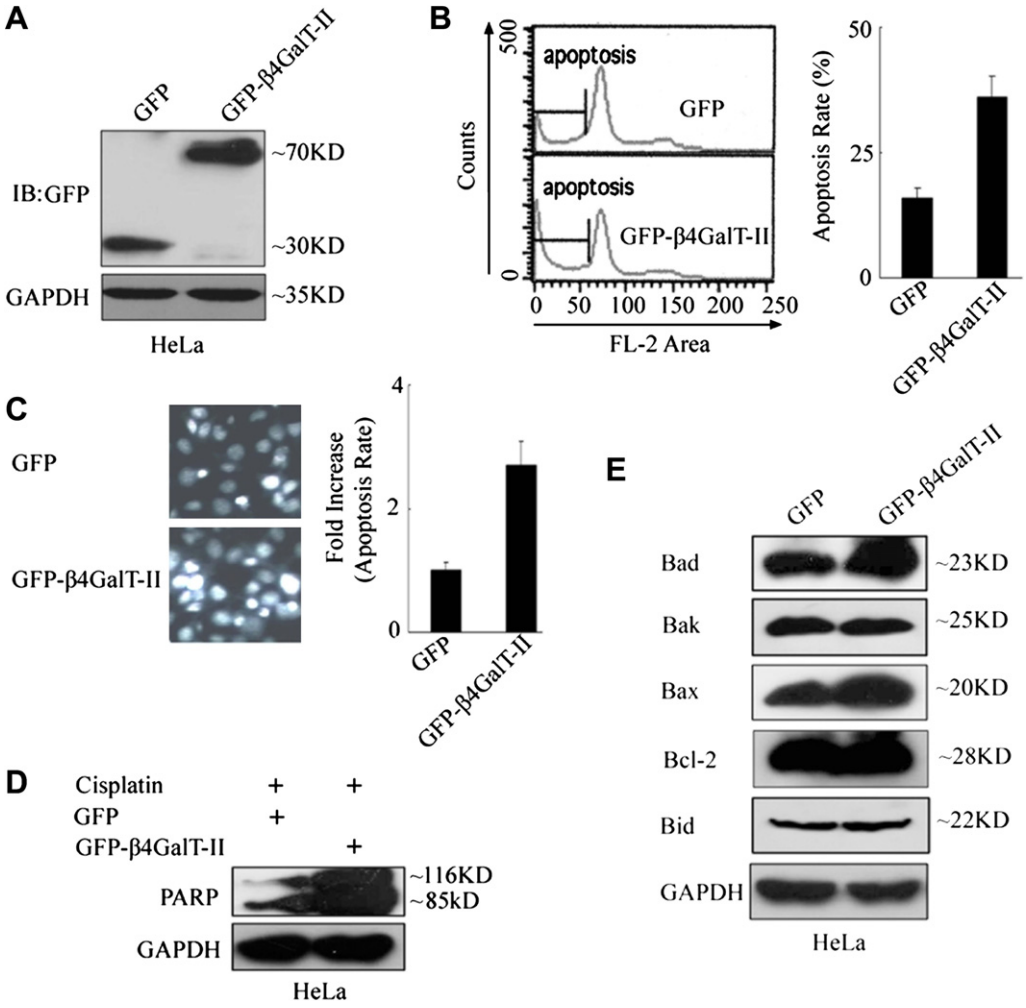

Fig. 2. Overexpression of β4GalT-II promotes cisplatin-induced apoptosis in HeLa cells. (A) HeLa cells were transiently transfected with GFP or GFP-tagged β4GalT-II expression plasmid and cell extracts were analyzed by immunoblotting with an anti-GFP antibody. GAPDH served as a loading control. (B) Cells transfected with GFP or GFP-tagged β4GalT-II expression plasmid were harvested after the treatment of control or cisplatin (5 μg/ml), fixed in ethanol, and stained with propidium iodide. The apoptotic rates were counted by flow cytometry analysis (left). Quantification of apoptotic cells was shown ($n = 3$; $p < 0.05$) (right). Each value was the mean ± SD of at least three independent experiments. (C) Hoechst 33258 staining of nuclei from HeLa cells transiently transfected with GFP or GFP-tagged β4GalT-II treated with cisplatin (5 μg/ml) for 24 h (left). At least 300 cells were counted from three different microscope fields and the percentage of apoptosis was standardized with that of HeLa cells untreated with cisplatin (right). Each value was the mean ± SD of at least three independent experiments. (D) Western blot analysis of PARP processing in total cell extracts of HeLa cells transiently transfected with GFP or GFP-tagged β4GalT-II expression vector treated with control or cisplatin (5 μg/ml) for 24 h. (E) Effect of β4GalT-II overexpression on the expression of Bcl-2 family members in HeLa cells. Western blot analysis of the expression of Bcl-2 family members in HeLa cells transiently transfected with GFP or GFP-tagged β4GalT-II expression plasmid with the indicated antibodies. The GAPDH Western blot served as a loading control.

domain (1–15 amino acids), a trans-membrane domain (15–32 amino acids) and a catalytic domain (32–372 amino acids) (Fig. 3A). To investigate the contribution of these domains in the pro-apoptotic role of β4GalT-II, the GFP-tagged deletion mutations were constructed (Fig. 3A), and transiently transfected into HeLa cells (Fig. 3B). FL(1–327aa), N(1–32aa) and C(15–327aa) were detected in the perinuclear spot that is similar to Golgi staining; however, GFP or D(15–32aa) were detected in the whole cell (Fig. 3C), indicating that the amino acid region between 15 and 32 was essential for the Golgi localization of β4GalT-II. To investigate the contribution of these domains in the pro-apoptotic role of β4GalT-II, HeLa cells transiently transfected with the indicated constructs were treated with cisplatin for 24 h, following Hoechst staining assay. As shown in Fig. 3D, compared to the controls, ectopic expression of FL(1–327aa), N(1–32aa) or C(15–327aa) construct increased cisplatin-induced apoptosis; however, the expression of D(15–32) construct had no significant effect on cisplatin-induced apoptosis. The same results were obtained from FACS assay (data not shown). Collectively, these results suggest that β4GalT-II promotes cisplatin-induced apoptosis in HeLa cells depending on its Golgi localization.

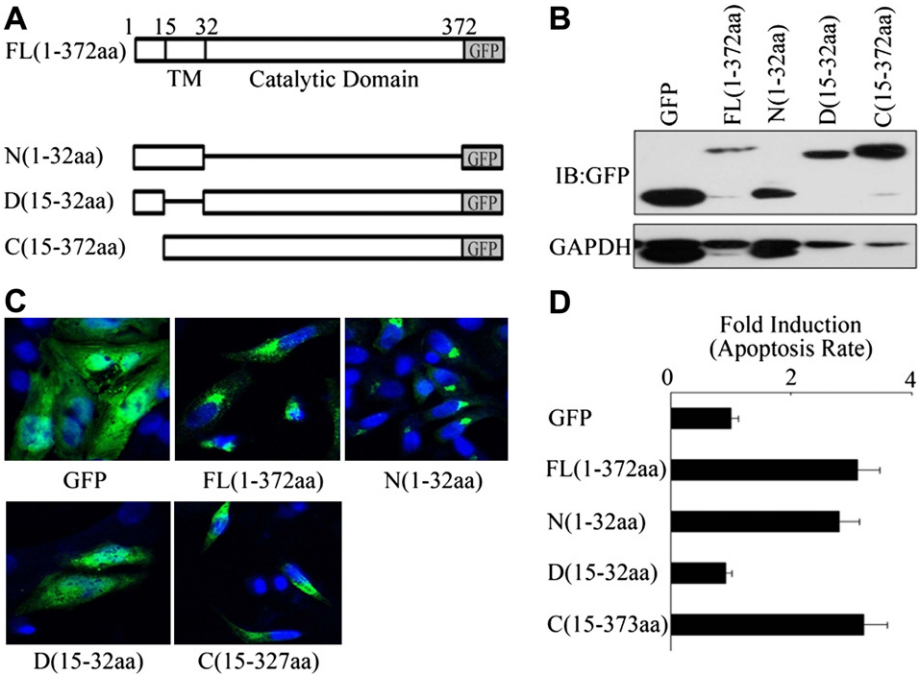

Fig. 3. β4GalT-II promotes cisplatin-induced apoptosis in HeLa cells depending on its Golgi localization. (A) A schematic diagram of GFP-tagged β4GalT-II construct (FL(1–327aa)) and its deletion mutation formats (N(1–32aa), C(15–327aa) and D(15–32aa)). (B) Western blot analysis of expression of GFP-tagged β4GalT-II construct and its deletion mutation in HeLa cells using anti-GFP antibody. The GAPDH Western blot served as a loading control. (C) HeLa cells transiently transfected with GFP-tagged β4GalT-II construct or its deletion mutation construct were stained with Hoechst 33258 and the localization of the indicated proteins was investigated using fluorescence microscope. (D) Hoechst 33258 staining of nuclei from HeLa cells transiently transfected with GFP, GFP-tagged β4GalT-II construct or its deletion mutation constructs treated with cisplatin (5 μg/ml) for 24 h. At least 300 cells were counted from three different microscope fields and the percentage of apoptosis was standardized with that of HeLa cells transiently transfected with GFP. Each value was the mean ± SD of at least three independent experiments.

The effect of β4GalTs overexpression on cisplatin-induced apoptosis in HeLa cells

To assess the specificity of the members of β4GalTs family in the regulation of cisplatin-induced apoptosis, EGFP-tagged β4GalTs expression plasmids were constructed and transiently transfected into HeLa cells. Forty-eight hour after transfection, EGFP expression was observed with Western blot using anti-GFP antibody. Consistent with previous report [19], the expression of exogenous β4GalT-VI was rarely detected in HeLa cells; however, the other members of β4GalTs were apparently expressed (Fig. 4A). Next, we investigated the effect of β4GalTs on apoptosis after cisplatin treatment for 24 h. Compared to that of the controls, the percentage of apoptotic cells in β4GalT-I to β4GalT-V or β4GalT-VII-overexpressed HeLa cells was markedly increased by FACS assay (Fig. 4B). This conclusion was further supported in Fig. 4C. Overexpression of β4GalT-I to β4GalT-V and β4GalT-VII sensitized HeLa cells to cisplatin-induced apoptosis as indicated by fragmented and condensed nuclei (Fig. 4C).

Discussion

β4GalT-II is a member of β1,4-galactosyltransferase (β4GalT) family which contribute in development and tumor behavior [12,14]. Since then, additional β4GalTs that medicate cell apoptosis have been reported [13,20–23]. In this report, we have described several observations that implicated the role of β4GalT-II in cisplatin-induced apoptosis in HeLa cells. (a) The ectopic expression of β4GalT-II in HeLa cells markedly accelerated cisplatin-induced apoptosis. (b) β4GalT-II played an important role in increasing the cleavage and expression of PARP. (c) Forced expression of β4GalT-II up-regulated pro-apoptosis proteins Bax and Bad expression. Taken together, our results suggest a pro-apoptotic role of β4GalT-II in HeLa cells. As described in the introduction, the expression of β4GalT-II was significantly altered in tumorigeness with unknown functions. To our knowledge, this is the first report of the contribution of β4GalT-II in tumor cells.

Bcl-2 family members are widely known to contribute in cell apoptosis [18]. Bax is a pro-apoptotic member of the Bcl-2 family [24]. The ratio of Bcl-2 to Bax protein might be the final determinant of whether a cell enters the execution phase of apoptosis and contribute in chemotherapy sensitivity [25,26]. β4GalT-II overexpression increased the expression of Bax without changing the expression of Bcl-2, resulting in induction of Bax:Bcl-2 ratio. Consistent with this, β4GalT-II overexpression increased the cleavage of PARP which is a target of Bax and contributes in cisplatin-induced apoptosis [27]. Furthermore, the mRNA expression of β4GalT-II was significantly reduced in

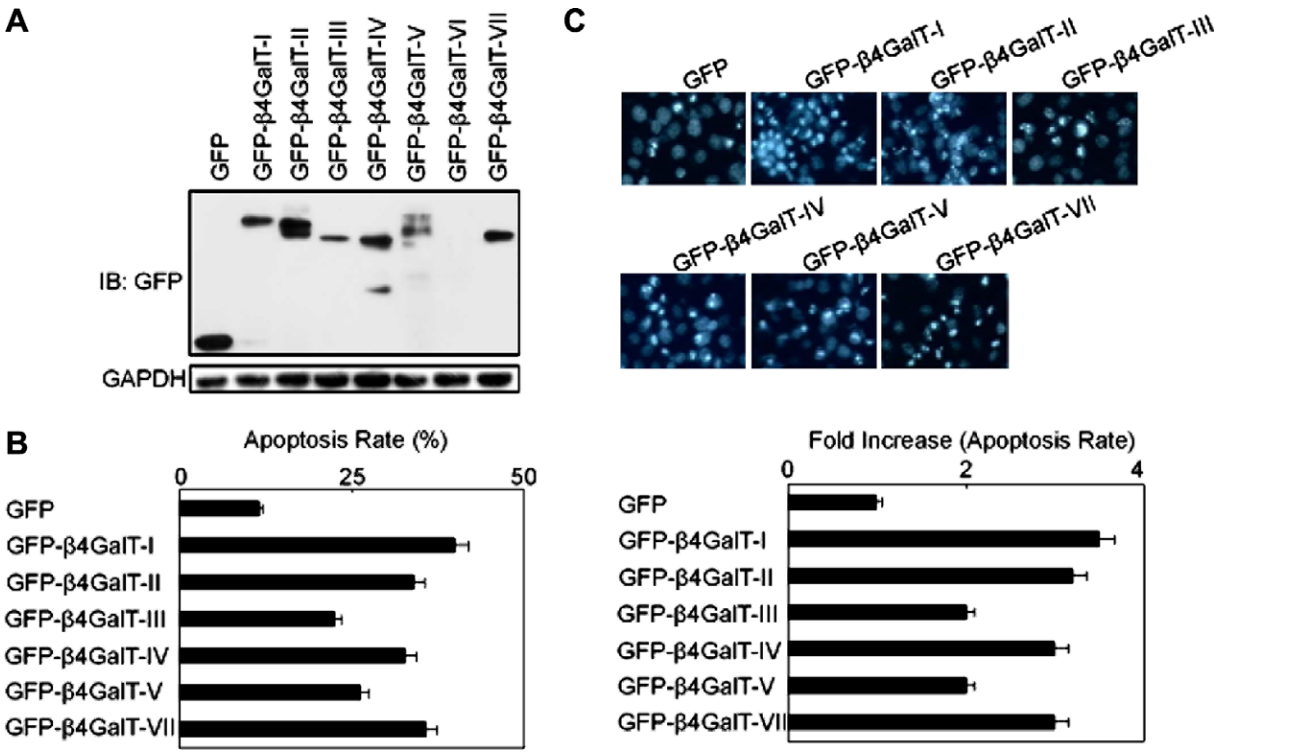

Fig. 4. The role of β4GalTs overexpression in cisplatin-induced apoptosis in HeLa cells. (A) HeLa cells were transiently transfected with GFP or GFP-tagged β4GalTs expression plasmid and cell extracts were analyzed by immunoblotting with an anti-GFP antibody. GAPDH served as a loading control. (B) Cells transfected with GFP or GFP-tagged β4GalTs expression plasmid were harvested after the treatment of control or cisplatin (5 μg/ml), fixed in ethanol, and stained with propidium iodide. The apoptotic rates were counted by flow cytometry analysis. Quantification of apoptotic cells was shown ($n = 3$; $p < 0.05$). Each value was the mean ± SD of at least three independent experiments. (C) Hoechst 33258 staining of nuclei from HeLa cells transiently transfected with GFP or GFP-tagged β4GalTs treated with cisplatin (5 μg/ml) for 24 h (upper). At least 300 cells were counted from three different microscope fields and the percentage of apoptosis was standardized with that of HeLa cells untreated with cisplatin (lower). Each value was the mean ± SD of at least three independent experiments.

response to cisplatin. Taken together, these data indicated that β4GalT-II might play an important role in cisplatin resistant and enhance the therapeutic efficiency of cisplatin for cervix cancer.

Another interesting finding of this study was that β4GalT-II promotes cisplatin-induced apoptosis in HeLa cells depending on its localization on Golgi. The Golgi complex is the central organelle of the secretory pathway and functions to posttranslationally modify newly synthesized proteins and lipids and sort them for transport to their sites of functions [28]. Similar to the endoplasmic reticulum stress response pathway, the Golgi complex may initiate signaling pathways to alleviate stress, and if irreparable, trigger apoptosis [29,30]. The targeting of Golgi complex of PKCdelta is an essential step in ceramide-induced apoptosis [31]. In this present, deletion the Golgi localization domain of β4GalT-II abolished its pro-apoptotic role in cisplatin-induced apoptosis, indicating the essential role of Golgi localization in the pro-apoptotic role of β4GalT-II. Furthermore, deletion of the catalytic domain of β4GalT-II had no effect on its pro-apoptotic role in cisplatin-induced apoptosis, indicating that the galactosylation activity of β4GalT-II was not contributed in its pro-apoptotic role. And, overexpression of β4GalT-I to β4GalT-V or β4GalT-VII significantly increased cisplatin-induced HeLa cell apoptosis, which indicated that a stress to Golgi by over-expression of β4GalT-II might contribute in its pro-apoptotic role in cisplatin-induced apoptosis.

In summary, we identified the pro-apoptotic role of β4GalT-II in the apoptosis response of HeLa cells to cisplatin. β4GalT-II overexpression increased HeLa cell apoptosis induced by cisplatin depending on its Golgi localization, which indicates that β4GalT-II might contribute in the therapeutic efficiency of cisplatin for cervix cancer. The mechanism of down-regulation of β4GalT-II in response to cisplatin and the pro-apoptotic role of β4GalT-II in HeLa cells should be further investigated.

Acknowledgments

This work was supported by National Natural Scientific Foundation of China (30470442 and 30330320) and CNHLPP (2004BA711A19) and a Grant from the Development of Science and Technology of Shanghai (02DJ14002).

References

[1] S. Nagata, Apoptosis by death factor, Cell 88 (1997) 355–365.
[2] Y.A. Hannun, Apoptosis and the dilemma of cancer chemotherapy, Blood 89 (1997) 1845–1853.
[3] A. Eastman, Activation of programmed cell death by anticancer agents: cisplatin as a model system, Cancer Cells 2 (1990) 275–280.
[4] D.S. Alberts, D. Garcia, N. Mason-Liddil, Cisplatin in advanced cancer of the cervix: an update, Seminars in Oncology 18 (1991) 11–24.
[5] G. Chu, Cellular responses to cisplatin. The roles of DNA-binding proteins and DNA repair, The Journal of Biological Chemistry 269 (1994) 787–790.
[6] N.W. Lo, J.H. Shaper, J. Pevsner, N.L. Shaper, The expanding beta 4-galactosyltransferase gene family: messages from the databanks, Glycobiology 8 (1998) 517–526.
[7] S. Guo, T. Sato, K. Shirane, K. Furukawa, Galactosylation of N-linked oligosaccharides by human beta-1,4-galactosyltransferases I, II, III, IV, V, and VI expressed in Sf-9 cells, Glycobiology 11 (2001) 813–820.
[8] N. Sasaki, H. Manya, R. Okubo, K. Kobayashi, H. Ishida, T. Toda, T. Endo, S. Nishihara, beta4GalT-II is a key regulator of glycosylation of the proteins involved in neuronal development, Biochemical and Biophysical Research Communications 333 (2005) 131–137.
[9] D. Zhou, C. Chen, S. Jiang, Z. Shen, Z. Chi, J. Gu, Expression of beta1,4-galactosyltransferase in the development of mouse brain, Biochimica et Biophysica Acta 1425 (1998) 204–208.
[10] K. Shirane, T. Sato, K. Segawa, K. Furukawa, Involvement of beta-1,4-galactosyltransferase V in malignant transformation-associated changes in glycosylation, Biochemical and Biophysical Research Communications 265 (1999) 434–438.
[11] S. Xu, X. Zhu, S. Zhang, S. Yin, L. Zhou, C. Chen, J. Gu, Overexpression of beta-1,4-galactosyltransferase I, II, and V in human astrocytoma, Journal of Cancer Research and Clinical Oncology 127 (2001) 502–506.
[12] X. Zhu, J. Jiang, H. Shen, H. Wang, H. Zong, Z. Li, Y. Yang, Z. Niu, W. Liu, X. Chen, Y. Hu, J. Gu, Elevated beta1,4-galactosyltransferase I in highly metastatic human lung cancer cells. Identification of E1AF as important transcription activator, The Journal of Biological Chemistry 280 (2005) 12503–12516.
[13] J. Jiang, J. Shen, T. Wu, Y. Wei, X. Chen, H. Zong, S. Zhang, M. Sun, J. Xie, X. Kong, Y. Yang, A. Shen, H. Wang, J. Gu, Down-regulation of beta1,4-galactosyltransferase V is a critical part of etoposide-induced apoptotic process and could be mediated by decreasing Sp1 levels in human glioma cells, Glycobiology 16 (2006) 1045–1051.
[14] J. Jiang, X. Chen, J. Shen, Y. Wei, T. Wu, Y. Yang, H. Wang, H. Zong, J. Yang, S. Zhang, J. Xie, X. Kong, W. Liu, J. Gu, Beta1,4-galactosyltransferase V functions as a positive growth regulator in glioma, The Journal of Biological Chemistry 281 (2006) 9482–9489.
[15] W.R. Sellers, D.E. Fisher, Apoptosis and cancer drug targeting, The Journal of Clinical Investigation 104 (1999) 1655–1661.
[16] S.W. Yu, H. Wang, M.F. Poitras, C. Coombs, W.J. Bowers, H.J. Federoff, G.G. Poirier, T.M. Dawson, V.L. Dawson, Mediation of poly(ADP-ribose) polymerase-1-dependent cell death by apoptosis-inducing factor, Science 297 (2002) 259–263.
[17] L. Tentori, A. Balduzzi, I. Portarena, L. Levati, P. Vernole, B. Gold, E. Bonmassar, G. Graziani, Poly (ADP-ribose) polymerase inhibitor increases apoptosis and reduces necrosis induced by a DNA minor groove binding methyl sulfonate ester, Cell Death and Differentiation 8 (2001) 817–828.
[18] A. Burlacu, Regulation of apoptosis by Bcl-2 family proteins, Journal of Cellular and Molecular Medicine 7 (2003) 249–257.
[19] T. Sato, K. Shirane, M. Kido, K. Furukawa, Correlated gene expression between beta-1,4-galactosyltransferase V and *N*-acetylglucosaminyltransferase V in human cancer cell lines, Biochemical and Biophysical Research Communications 276 (2000) 1019–1023.
[20] S. Zhang, M. Cai, S.W. Zhang, Y. Hu, J.X. Gu, Involvement of beta 1,4 galactosyltransferase 1 and Gal beta1–>4GlcNAc groups in human hepatocarcinoma cell apoptosis, Molecular and Cellular Biochemistry 243 (2003) 81–86.
[21] X. Zhu, S. Chen, X. Yin, A. Shen, S. Ji, Z. Shen, J. Gu, Constitutively active PKB/Akt inhibited apoptosis and down-regulated beta1,4-galactosyltransferase 1 in hepatocarcinoma cells, Biochemical and Biophysical Research Communications 309 (2003) 279–285.
[22] L. de la Cruz, K. Steffgen, A. Martin, C. McGee, H. Hathaway, Apoptosis and involution in the mammary gland are altered in mice lacking a novel receptor, beta1,4-Galactosyltransferase I, Developmental Biology 272 (2004) 286–309.
[23] Z. Li, H. Wang, H. Zong, Q. Sun, X. Kong, J. Jiang, J. Gu, Downregulation of beta1,4-galactosyltransferase 1 inhibits CDK11(p58)-mediated apoptosis induced by cycloheximide, Biochemical and Biophysical Research Communications 327 (2005) 628–636.
[24] M. Crompton, Bax, Bid and the permeabilization of the mitochondrial outer membrane in apoptosis, Current Opinion in Cell Biology 12 (2000) 414–419.
[25] Y. Takagi-Morishita, N. Yamada, A. Sugihara, T. Iwasaki, T. Tsujimura, N. Terada, Mouse uterine epithelial apoptosis is associated with expression of mitochondrial voltage-dependent anion channels, release of cytochrome C from mitochondria, and the ratio of Bax to Bcl-2 or Bcl-X, Biology of Reproduction 68 (2003) 1178–1184.
[26] A. Leri, P.P. Claudio, Q. Li, X. Wang, K. Reiss, S. Wang, A. Malhotra, J. Kajstura, P. Anversa, Stretch-mediated release of angiotensin II induces myocyte apoptosis by activating p53 that enhances the local renin-angiotensin system and decreases the Bcl-2-to-Bax protein ratio in the cell, The Journal of Clinical Investigation 101 (1998) 1326–1342.
[27] P.A. Nguewa, M.A. Fuertes, V. Cepeda, C. Alonso, C. Quevedo, M. Soto, J.M. Perez, Poly(ADP-ribose) polymerase-1 inhibitor 3-aminobenzamide enhances apoptosis induction by platinum complexes in cisplatin-resistant tumor cells, Medicinal Chemistry (Shariqah, United Arab Emirates) 2 (2006) 47–53.
[28] J.D. Jamieson, The Golgi complex: perspectives and prospectives, Biochimica et Biophysica Acta 1404 (1998) 3–7.
[29] K. Nozawa, C.A. Casiano, J.C. Hamel, C. Molinaro, M.J. Fritzler, E.K. Chan, Fragmentation of Golgi complex and Golgi autoantigens during apoptosis and necrosis, Arthritis Research 4 (2002) R3.
[30] C.E. Machamer, Golgi disassembly in apoptosis: cause or effect? Trends in Cell Biology 13 (2003) 279–281.
[31] T. Kajimoto, Y. Shirai, N. Sakai, T. Yamamoto, H. Matsuzaki, U. Kikkawa, N. Saito, Ceramide-induced apoptosis by translocation, phosphorylation, and activation of protein kinase Cdelta in the Golgi complex, The Journal of Biological Chemistry 279 (2004) 12668–12676.