Circulating galectin-3 in the bloodstream: An emerging promoter of cancer metastasis

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Abstract

Increased concentrations of free circulating galectin-3 are commonly seen in the blood circulation of patients with many types of cancers including colorectal cancer. Recent studies have shown that changes in circulating galectin-3 levels in cancer patients may contribute significantly to the metastatic spread of disseminating cancer cells by enhancing their ability to adhere to blood vessel endothelium and by helping their avoidance of immune surveillance. Thus, targeting the galectin-3 actions in the circulation may hold significant promise for future development of novel therapeutic agents to prevent metastasis and reduce cancer-associated fatality.

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INTRODUCTION

Galectin-3 is a galactoside-binding, small molecular weight (about 30 kDa) protein that is expressed in many types of human cells, in particular epithelial and immune cells. As a multi-functional protein with multiple cellular localizations, galectin-3 is over-expressed and abnormally localized in many types of human cancers and has attracted significant interest in cancer research over the past decades.

CELL-ASSOCIATED GALECTIN-3

Many earlier investigations were focused on the expression and roles of the cell-associated form of galectin-3. Galectin-3 is synthesized in the cytoplasm as a cytosolic protein but can be transported to multiple subcellular localizations in the cell nucleus, to the cell surface or can be secreted to the outside of cells. Cytoplasmic galectin-3 functions as an apoptosis inhibitor by suppressing mitochondrial depolarization and preventing the release of cytochrome C, while nuclear galectin-3 acts as a mRNA splicing promoter, and in contrast to cytoplasmic galectin-3, has pro-apoptotic activity. Loss of galectin-3 nuclear localization and its accumulation in the cytoplasm is commonly seen in many types of human cancers, including colorectals, prostate and tongue carcinoma. Change in galectin-3 localization from the nuclei to the cytoplasm closely correlates with tumour progression. In vitro studies have shown that accumulation of galectin-3 in the cytoplasm by stable galectin-3 gene transfection increases cancer cell invasion and promotes tumour angiogenesis.
Cell surface-associated extracellular galectin-3 interacts with basement matrix glycans (e.g. laminin and fibronectin) and promotes tumour cell release from the primary tumour sites by increasing tumour cell adhesion and invasion[14]. Over expression of the cell surface-associated galectin-3 in epithelial cancer cells increases the interaction of cancer cells with galactoside-terminated glycans expressed on the surface of adjacent cells and promotes cancer cell homotypic aggregation and heterotypic adhesion to endothelium in cancer cell haematogenous dissemination[10,11]. The cell surface-associated galectin-3 has also been shown to be required in stabilization of epithelial-endothelial interaction networks during cancer cell extravasation[22]. Suppression of galectin-3 expression in melanoma cells reduces tumour cell invasiveness and capacity to form tube-like structures on collagen[13], while suppression of galectin-3 expression in metastatic human colon[14] and breast[15] cancer cells before inoculation of the cells into nude mice results in significant reduction of tumour growth and metastasis.

**CIRCULATING GALECTIN-3 IN THE BLOODSTREAM**

Galectin-3 is also found in the bloodstream. While little is known of a physiological role for free galectin-3 in the circulation of healthy people, recent investigations have shown that the concentrations of circulating galectin-3 is significantly increased in the bloodstream of cancer patients. For example, up to 5-fold increase of galectin-3 concentration was reported in the sera of patients with colorectal cancer[18]. Compared to healthy people, galectin-3 concentration was also significantly higher in the serum of patients with breast, lung[19], head and neck[20] cancers and melanoma[21]. Furthermore, patients with metastatic disease have higher concentrations of circulating galectin-3 than those with localized tumours. The source of increased serum galectin-3 in cancer patients remains unknown but has been speculated to be generated by the tumour cells as well as the peri-tumoural inflammatory and stromal cells[22].

Recently, it has been revealed that introduction of recombinant galectin-3 at pathologically-relevant circulating galectin-3 concentrations induces a significant increase of cancer (such as colon and breast cancer and melanoma) cell adhesion to both macro- and micro-vascular endothelial cells in vitro under static as well as fluid flow conditions[23]. These effects of galectin-3 are thought to be related to the binding of galectin-3 to the Thomson-Friedenreich carbohydrate (galactose β1, 3N-acetylgalactosamine-, TF) antigen expressed by the transmembrane mucin protein MUC1[19].

The TF antigen is the core 1 structure of O-linked mucin type glycans. Unsubstituted TF antigen does not appear in normal epithelial cells but is found in over 90% of all types of human cancer cells studied[24]. The increased expression of TF antigen is one of the most common glycosylation alterations in human cancer. The transmembrane mucin protein MUC1 is a large and heavily glycosylated (up to 50% of the molecular weight) protein that is over-expressed (up to 10-fold) and is aberrantly glycosylated in most epithelial cancer cells[25]. It is one of the major cell surface glycoproteins that carry the unsubstituted TF antigen in gastric and colorectal adenocarcinomas[22,23]. The increased occurrence of TF antigen and the increased expression of MUC1 are each independently associated with high metastatic potential and poor prognosis in several types of human cancers, including colorectal and breast cancers[24,26].

Earlier investigations have shown that MUC1 protrudes over 10 times higher from the cell surface than the typical cell surface adhesion molecules[24] and promotes tumour cell release from the primary tumour sites by inhibiting E-Cadherin-mediated cell-cell and integrin-mediated cancer-matrix interactions[27,28]. It has recently been shown that the huge size and length of MUC1 form a protective shield around the cell surface and prevent adhesion of cancer cells to endothelial cells[20]. Binding of galectin-3 to cancer-associated MUC1 breaks up the protective shield of MUC1 by causing MUC1 cell surface polarization and the subsequent exposure of the cell adhesion molecules, including CD44 and ligand(s) to endothelial-associated E-selectin, which results in adhesion of the cancer cells to endothelial cells. As is the increased expression of MUC1 by cancer cells, the increased expression of the galectin-3-ligand TF antigen by cancer-associated MUC1 and increased circulation of galectin-3 are all common features in cancer. It is most likely that an increased interaction between circulating galectin-3 and cancer-associated MUC1 in the bloodstream of cancer patients enhances disseminating cancer cell adhesion to the blood vessel endothelium, which then promotes cancer cell haematogenous spread to remote metastasis sites. This is supported by the in vivo experimental metastasis assays that showed pre-treatment of the MUC1 positively-, but not negatively-, transfected human melanoma cells with recombinant galectin-3 before inoculation of the cells into immune deficient mice causes significant reduction of metastasis-associated animal survival[29].

Free circulating galectin-3 may also be involved in the regulation of T cell activity and may play a role in the inhibition of anti-tumour immunity[29]. T cells play a critical role in cancer immune surveillance for the control and destruction of tumour cells[30]. Cell surface binding of soluble galectin-3 has been shown to activate tumour-reactive T cells to produce immunosuppressive cytokines (e.g. IFNγ) and to induce T cell apoptosis. Interestingly, these effects of galectin-3 are seen to occur only in tumour-experienced but not naïve T cells, indicating that initial T cell receptor activation may induce changes in cell surface glycosylation in antigen-experienced T cells that make such T cells more sensitive to galectin-3 binding and activation. The concentrations of soluble galectin-3 for T cell activation and apoptosis induction in these studies usually occur at ≥ 25 μg/mL, which are much higher than...
the concentrations of the circulating galectin-3 in cancer patients. However, cell surface binding of galectin-3 often induces clustering of the cell surface receptors. There is evidence that clustering of galectin-3 receptors could enhance the galectin-3 binding affinity by as much as 10 000-fold. Thus, it is possible that a higher galectin-3 concentration could be achieved at a local galectin-3 binding site/microenvironment in the circulation that would allow galectin-3 to drive tumour-reactive T cell activation and apoptosis and, therefore, help the avoidance of tumour cell destruction by immune surveillance.

CONCLUSION

Recent investigations have demonstrated that increased levels of free circulating galectin-3 in the blood circulation of cancer patients may play an important role in promoting disseminating cancer cell survival and haematogenous spread to remote tumour sites. This implies that targeting the actions of circulating galectin-3 in the blood circulation may have significant implications for the development of novel therapeutic agents to prevent metastasis and reduce cancer-associated high fatality.

REFERENCES

1. Takenaka Y, Fukumori T, Raz A. Galectin-3 and metastasis. Glycobiology 2004; 19: 543-549
2. Liu FT, Rabinovich GA. Galectins as modulators of tumour progression. Nat Rev Cancer 2005; 5: 29-41
3. Yu F, Finley RL Jr, Raz A, Kim HR. Galectin-3 translocates to the perinuclear membranes and inhibits cytochrome c release from the mitochondria. A role for synxin in galectin-3 translocation. J Biol Chem 2002; 277: 15919-15927
4. Dagher SF, Wang JL, Patterson RJ. Identification of galectin-3 as a factor in pre-mRNA splicing. Proc Natl Acad Sci USA 1995; 92: 1213-1217
5. Califice S, Castronovo V, Bracke M, van den Brule F. Dual activities of galectin-3 in human prostate cancer: tumor suppression of nuclear galectin-3 vs tumor promotion of cytoplasmic galectin-3. Oncogene 2004; 23: 7527-7536
6. Lotz MM, Andrews CW Jr, Korzelius CA, Lee EC, Steele GD Jr, Clarke A, Mercurio AM. Decreased expression of Mac-2 (carbohydrate binding protein 35) and loss of its nuclear localization are associated with the neoplastic progression of colon carcinoma. Proc Natl Acad Sci USA 1993; 90: 3466-3470
7. Sanjuán X, Fernández PL, Castells A, Castronovo V, van den Brule F, Liu FT, Cardesa A, Campo E. Differential expression of galectin-3 and galectin 1 in colorectal cancer progression. Gastroenterology 1997; 113: 1906-1915
8. van den Brule FA, Walsregen D, Liu FT, Castronovo V. Alteration of the cytoplasmic/nuclear expression pattern of galectin-3 correlates with prostate carcinoma progression. Int J Cancer 2000; 89: 361-367
9. Honjo Y, Nangia-Makker P, Inohara H, Raz A. Down-regulation of galectin-3 suppresses tumorigenicity of human breast carcinoma cells. Clin Cancer Res 2001; 7: 661-668
10. Khaldoyanidi SK, Glinsky VV, Sikora L, Glinski AB, Mossine VV, Deutscher SL, Pienta KJ, Quinn TP. Intravascular metastatic cancer cell homotypic aggregation at the sites of primary attachment to the endothelium. Cancer Res 2003; 63: 3805-3811
11. Shekhar MP, Nangia-Makker P, Tait L, Miller F, Raz A. Alterations in galectin-3 expression and distribution correlate with breast cancer progression: functional analysis of galectin-3 in breast epithelial-endothelial interactions. Am J Pathol 2004; 165: 1931-1941
12. Mourad-Zeidan AA, Melnikova VO, Wang H, Raz A, Bar-Eli M. Expression profiling of Galectin-3-depleted melanoma cells reveals its major role in melanoma cell plasticity and vasculogenic mimicry. Am J Pathol 2008; 173: 1839-1852
13. Bresalier RS, Mazurek N, Sternberg LR, Byrd JC, Yunker CK, Nangia-Makker P, Raz A. Metastasis of human colon cancer is altered by modifying expression of the beta-galactoside-binding protein galectin 3. Gastroenterology 1998; 115: 287-296
14. Iurisci I, Tinari N, Nolati C, Angelucci D, Cianchetti E, Iacobelli S. Concentrations of galectin-3 in the sera of normal controls and cancer patients. Clin Cancer Res 2000; 6: 1389-1393
15. Saussesse S, Lorfevre F, Lequeux T, Laurent G, Chantrain R. Galectin-3 interaction with Thomsen-Friedenreich disaccharide on cancer-associated MUC1 causes increased cancer cell endothelial adhesion. Oral Oncol 2008; 44: 86-93
16. Vereeken P, Zouaoui Boudjeltia K, Debray C, Awada A, Legssyer I, Sales F, Petein M, Vanhaeverbeek M, Ghahem M, Heenen M. High serum galectin-3 in advanced melanoma: preliminary results. Clin Exp Dermatol 2006; 31: 105-109
17. Zhao Q, Guo X, Nash GB, Stone PC, Hilkers J, Rhodes JM, Yu LG. Circulating galectin-3 promotes metastasis by modifying muc1 localization on cancer cell surface. Cancer Res 2009; 69: 6799-6806
18. Yu LG, Andrews N, Zhao Q, McKeon D, Williams JF, Connor LJ, Gerasimenko OV, Hilkers J, Hirabayashi J, Kasai K, Rhodes JM. Galectin-3 interaction with Thomsen-Friedenreich disaccharide on cancer-associated MUC1 causes increased cancer cell endothelial adhesion. J Biol Chem 2007; 282: 773-781
19. Yu LG. The oncofetal Thomsen-Friedenreich carbohydrate antigen in cancer progression. Glycobiology 2007; 24: 411-420
20. Taylor-Papadimitriou J, Burchell J, Miles DW, Dalziel M. MUC1 and cancer. Biochim Biophys Acta 1999; 1455: 301-313
21. Baldus SE, Hanisch FG, Koltsakis GM, Zirbes TK, Thiele J, Isenberg J, Karsten UR, Devine PL, Dienes HP. Coexpression of MUC1 mucin peptide core and the Thomsen-Friedenreich antigen in colorectal neoplasms. Cancer 1998; 82: 1019-1027
22. Baldus SE, Hanisch FG, Monaca E, Karsten UR, Zirbes TK, Thiele J, Dienes HP. Immunoreactivity of Thomsen-Friedenreich (TF) antigen in human neoplasms: the importance of carrier-specific glycoprote on cancer MUC1. Histol Histopathol 1999; 14: 1153-1158
23. Nakamori S, Ota DM, Cleary KR, Shirotani K, Irimura T. MUC1 mucin expression as a marker of progression and metastasis of human colorectal carcinoma. Gastroenterology 1994; 106: 353-361
24. Baldus SE, Zirbes TK, Hanisch FG, Kunze D, Shafizadeh ST, Nolden S, Möng SP, Schneider PM, Karsten U, Thiele J, Hölscher AH, Dienes HP. Thomsen-Friedenreich antigen presents as a factor in pre-mRNA splicing. Trends Biochem Sci 1992; 17: 359-363
25. Wesseling J, van der Valk SW, Hilken J. A mechanism for inhibition of E-cadherin-mediated cell-cell adhesion by the membrane-associated mucin epsilon-MUC1. Mol Biol Cell 1996; 7: 565-577
26. Wesseling J, van der Valk SW, Vos HL, Sonnenberg A, Hilkens J. Epispalin (MUC1) overexpression inhibits integrin-mediated metastasis of human breast carcinoma. WJG 2010; 6: 179-186

Yu LG. Circulating galectin-3 promotes metastasis
Yu LG. Circulating galectin-3 promotes metastasis

cell adhesion to extracellular matrix components. J Cell Biol 1995; 129: 255-265

29 Peng W, Wang HY, Miyahara Y, Peng G, Wang RF. Tumor-associated galectin-3 modulates the function of tumor-reactive T cells. Cancer Res 2008; 68: 7228-7236

30 Ostrand-Rosenberg S. Immune surveillance: a balance between protumor and antitumor immunity. Curr Opin Genet Dev 2008; 18: 11-18

31 Stillman BN, Hsu DK, Pang M, Brewer CF, Johnson P, Liu FT, Baum LG. Galectin-3 and galectin-1 bind distinct cell surface glycoprotein receptors to induce T cell death. J Immunol 2006; 176: 778-789

32 Nieminen J, Kuno A, Hirabayashi J, Sato S. Visualization of galectin-3 oligomerization on the surface of neutrophils and endothelial cells using fluorescence resonance energy transfer. J Biol Chem 2007; 282: 1374-1383

33 Dam TK, Gabius HJ, André S, Kaltner H, Lensch M, Brewer CF. Galectins bind to the multivalent glycoprotein asialofetuin with enhanced affinities and a gradient of decreasing binding constants. Biochemistry 2005; 44: 12564-12571

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