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Carbohydrate Antigens as Cancer-Initiating Cell Markers

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1. Introduction

The hypothesis that cancer-initiating cells are a prerequisite for cancer ontogenesis is now widely accepted. The existence of cancer-initiating cells is well documented in brain, lung, and breast cancers (Boman et al., 2008; Takaishi et al., 2009), as well as in other malignancies. Cancer-initiating cells (CIC) exhibit low proliferative rates, self-renewing capacity, a propensity to differentiate into actively proliferating tumour cells, and show resistance to chemotherapy or radiation (Vander Griend et al., 2008; Sell & Leffert, 2008). Since cancer-initiating cells clearly differ from the majority of cells of the tumour mass, studying the expression and function of surface molecules on cancer-initiating cells is an important aspect of tumor biology.

A great number of more or less specific surface molecules of cancer-initiating cells have been described during recent years. Among the markers most widely accepted is CD44 (Shipitsin et al., 2007; Ponnusamy & Batra, 2008). CD44 is a cell surface type I transmembrane glycoprotein involved in cell-cell interactions, cell adhesion, and migration. It is a receptor for hyaluronic acid, but can also interact with other ligands (Marhaba & Zöller, 2004). CD44 was found to be expressed on cancer-initiating cells in gastric cancer (Takaishi et al., 2009). A single $CD44^+$ cell from a colorectal tumour could form a sphere in vitro and was able to generate a xenograft tumour resembling the properties of the primary tumour (Du et al., 2008). CD133 is also a widely recognized marker of cancer-initiating cells. CD133 was initially described as a surface antigen specific for human haematopoietic stem cells and as a marker for murine neuroepithelial and several other embryonic epithelia (Singh et al., 2004). In a number of recent studies, CD133 alone or in combination with other markers was used for the isolation of CIC from malignant tumours of colon, lung and liver (Haraguchi et al., 2008). $CD133^+$ tumour cells repair radiation-induced DNA damage more effectively than $CD133^-$ tumour cells (Bao et al., 2006). CD133 is an independent prognostic marker that correlates with poor overall survival in patients with malignancies (Horst et al., 2008).

2. Carbohydrate antigens as cancer-initiating cell markers

Almost all CIC markers described so far are proteins. Carbohydrate CIC markers have been rarely reported (Son et al., 2009). This is surprising, because some of them are known as "stage-specific embryonic antigens" for a long time (Solter & Knowles, 1978), and because many carbohydrate epitopes are known as tumour markers (Hakomori, 1989). We consider carbohydrate antigens as biologically active entities, which may indicate or even be actively involved in the fundamental functional changes during the transformation of an ordinary epithelial cell into a carcinoma cell, as well as in the process of tumour progression (Cao et al., 1997). Changes in glycosylation may provide diagnostic markers and therapeutic targets. CD173 (Blood group antigen H type 2, H2), CD174 (Lewis Y, LeY) and CD176 (Thomsen-Friedenreich antigen, core-1) are known to be developmentally regulated carbohydrate antigens which are expressed to a varying degree on many human carcinomas. We have found that CD173, CD174 and CD176 were expressed on $CD34^+$ malignant human hematopoietic cells (Cao et al., 2001; 2008). In current studies, we found the expression of CD173, CD174 and CD176 on cancer-initiating cells of several epithelial cancers (Lin et al. 2010a; 2010b).

2.1 CD173 and CD174 as markers of cancer-initiating cells

ABH and Lewis (Le) blood group antigens are cell surface carbohydrate structures. Besides their expression on erythrocytes, they are also widely distributed in body fluids and normal tissues, especially on epithelia of glandular tissues. H2 (Fucα1-2Gal-β1-4GlcNAcβ1-) and LeY (Fucα1-2Gal-β1-4[Fucα1-3]GlcNAcβ1-) are fucosylated derivatives of the same type 2 precursor carbohydrate chain found on glycoproteins. H2 is synthesized by the addition of a fucose to the type 2 precursor chain mediated by α1-2 fucosyltransferase encoded by the H gene. LeY results from the additional action of α1-3 fucosyltransferase encoded by the LeX gene. Histo-blood group antigens H2 and LeY were assigned as CD173 and CD174, respectively, during the Seventh Workshop and Conference on Human Leucocyte Differentiation Antigens in Harrogate in June 2000 (Cao et al., 2002a). In this chapter we use the new designations for these oligosaccharide structures (Figure 1).

A number of studies have shown that abnormal expression of CD173 and CD174 occurs in epithelial malignancies (Fujitani et al., 2000; Baldus et al., 2006). We have found that CD173 and CD174 were expressed on $CD34^+$ haematopoietic progenitor cells (Cao et al., 2001). Moreover, fucosylated histo-blood group antigens (H antigens) were co-expressed on CD44v6 after transfection of α(1-2)fucosyltransferase concomitant with an enhanced tumorigenicity in rat colon adenocarcinoma cells (Goupille et al., 1997). In our current study, immunocytological staining and flow cytometric analysis were performed to investigate the co-expression of CD173 or CD174 with CD44 on breast cancer cells. We observed that CD44 together with CD173 or CD174 are located at the cell surface and reveal co-expression in a significant proportion of cultured breast cancer cells and in tissue specimens taken from breast cancer.

Tamoxifen (4-OHT) which is an oestrogen receptor ligand, was reported to induce G0/G1 growth arrest and to inhibit the proliferation of breast cancer cells. A recent study showed that 4-OHT treatment increased the number of mammary cancer stem cell-like cells (Mani et al., 2008). To assess whether CD44, CD173, and CD174 expression is simultaneously affected after exogenous treatment, we treated the breast cancer culture cells with 4-OHT. In semiquantitative flow cytometric analysis, the number of $CD44^+/CD173^+$ or $CD44^+/CD174^+$ breast cancer cells could be enhanced in cultured cells after 4-OHT treatment (Figure 1). Therefore, we conclude that CD44 is co-expressed with CD173 and CD174 in breast cancer.

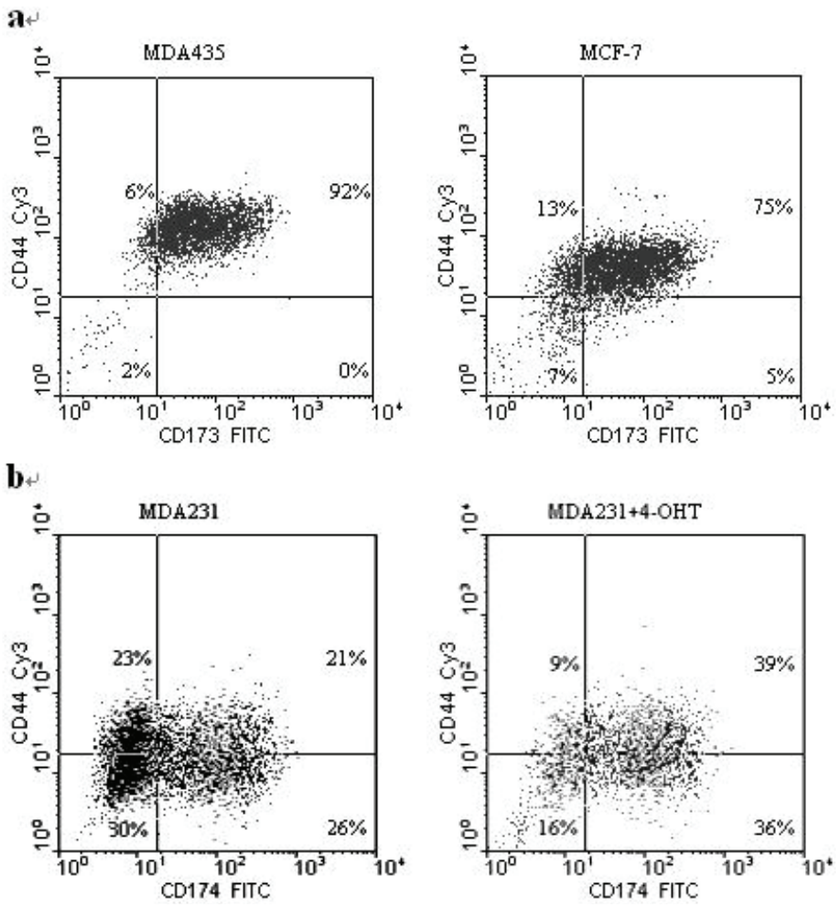


Fig. 1. a: Flow-cytometric analysis of $CD44^+/CD173^+$ expression in the breast adenocarcinoma cell lines MDA-MB-435 and MCF-7. Cancer cells were incubated with anti-CD44 (IgG2b) and anti-CD174 (IgM) antibodies, respectively, followed by incubation with anti-IgG-Cy3 (γ chain-specific) and anti-IgM-FITC (μ chain-specific). Values are taken from one of three similar experiments. Large proportions of both cell lines are positive for both markers (CD44 and H2). b: Flow-cytometric analysis of $CD44^+/CD174^+$ expression on MDA-MB-231 cells before and after 4-OHT treatment. 4-OHT treatment results in an increase in the proportion of cells expressing both CD44 and CD174 (LeY). Values are taken from one of three similar experiments (from Lin et al. 2010a)

CD133 is also a marker of cancer-initiating cells. We found that CD133 was indeed co-expressed with CD173 and CD174, although at a lower percentage (<5% of the total cancer cells). The manifestation of the lower percentage was due to the smaller subpopulation of cancer cells possessing CD133 (<5%). In addition, we found that cases with increased CD173 and CD174 expression correlated with raised CD133 expression.

An interesting observation was the strong staining for CD173 of myoepithelial/basal cells in cases of intraductal breast carcinomas (Figure 2.). In normal ducts of transitional tissues of the same sections, the basal cell layer was only occasionally positive for CD173 (Karsten et al., 1993). At present, we cannot explain the cause and significance of this observation. Since H and LeY antigens are developmentally regulated antigens, this phenomenon might also be indicative of an ongoing epithelial-mesenchymal transition of these cells.

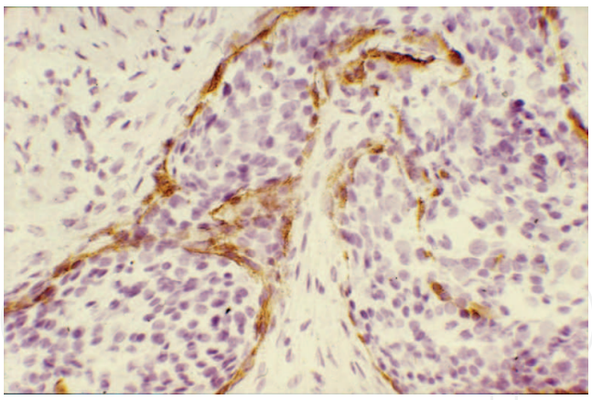


Fig. 2. Immunohistochemistry of an intraductal carcinoma section stained with the CD173 antibody A46-B/B10. Basal cells (stem cell-like cells) of the remaining duct walls are strongly stained.

Type 2-based ABH oligosaccharides are carried on several different glycoproteins and glycolipids (Hakomori et al., 1981). In epithelial ovarian cancer, the major carrier proteins of CD174 are CA125 and MUC1 (Yin et al., 1996). In $CD34^+$ hematopoietic stem cells, the major carrier of CD173 and CD174 is a 170-kDa glycoprotein (Cao et al., 2001). CD44 is also a carrier of H antigens in the rat PRO cell line (Rapoport et al., 1999). In our studies, potential glycoproteins carrying CD173 or CD174 were analyzed in three breast carcinoma cell lines by immunoprecipitation and in a sandwich ELISA. The CD44 immunoprecipitate from the lysates of the three cell lines was subjected to immunoblot analysis using CD173 and CD174 antibodies. Both antibodies stained the CD44 band (Figure 3). In a new sandwich solid-phase enzyme-linked immunosorbent assay (ELISA) with anti-CD44 as capture antibody, followed by CD173 or CD174 antibodies, respectively, both antibodies scored positive in all three cell lines examined, indicating that CD173 and CD174 epitopes are expressed on the CD44 molecule.

It is believed that CD173 and CD174 structures on glycoprotein expressed by carcinomas contribute to adhesion, cell aggregation, invasion, and metastasis. CD174 is involved in early cell-cell contacts during tumor-associated angiogenesis (Moehler et al., 2008). CD173 and CD174 are apparent markers of the degree of malignancy in cancer patients (Fujitani et al., 2000; Steplewska-Mazur et al., 2000). Higher expression of CD173 and CD174 was more often found in patients with high grade tumours and poor prognosis compared to those with better prognosis (Baldus et al., 2006). In lymph node negative breast carcinomas, over-expression of CD174 was associated with significantly decreased patient survival (Madjd et al., 2005). Increased tumorigenicity mediated by α1-2 fucosylation is associated with increased resistance to apoptosis and escape from immune control (Rapoport et al., 1999; Goupille et al., 2000). All these phenomena may be associated with the expression of CD173 and CD174 on cancer-initiating cells.

Failure of current cancer therapies may be ascribed to the inefficacy of drugs on potentially quiescent cancer-initiating cells. Treatment strategies therefore need to consider the presence of cancer-initiating cells. The high expression of CD173 and especially of CD174 on the surface of cancer-initiating cells in breast carcinomas suggests that these antigens could be potential targets for antibody-mediated diagnosis and therapy. Anti-LeY antibodies have already been tried in adjuvant cancer therapy (Stahel et al., 1992). More recent studies have demonstrated that the administration of low doses of anti-CD174 antibodies may lead to an

effective anti-tumour response, even without induction of TNF-α release (Dettke et al., 2000), and anti-CD174 antibody conjugated with doxorubicin is presently under evaluation in the therapy of epithelial tumours (Tolcher et al., 1999).

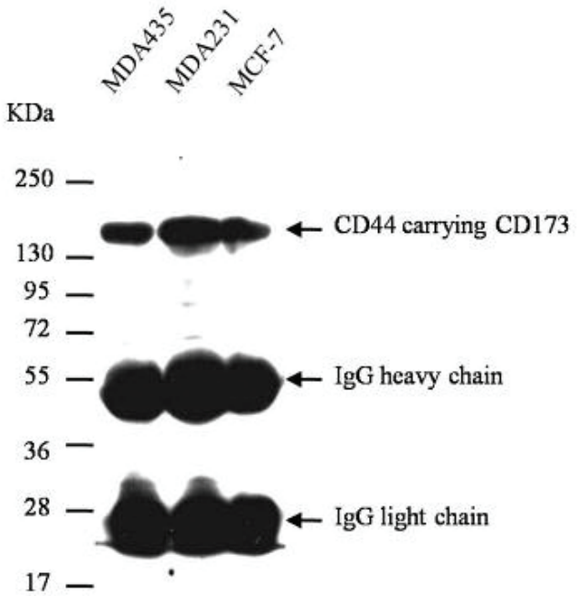


Fig. 3. Immunoprecipitation of lysates from breast adenocarcinoma cell lines MDA-MB-231, MDA-MB-435, and MCF. The CD44-immunoprecipitated material was resolved by SDS-PAGE and analyzed by immunoblotting using mAb CD173. The data show that in breast carcinomas CD44 is carrying CD173 (H2) (from Lin et al. 2010a)

2.2 CD176 as a marker of cancer-initiating cells

The Thomsen-Friedenreich antigen (TF, or CD176) is a tumour-associated carbohydrate epitope with the structure Galb1-3GalNAca1-O-. While this disaccharide is a ubiquitous core structure (core-1) found in a cryptic manner on many membrane glycoproteins of normal cells, its exposure on tumour cells is obviously restricted to a few specific carrier proteins. TF was assigned as CD176 during the Seventh Workshop and Conference on Human Leucocyte Differentiation Antigens in Harrogate in June 2000 (Cao et al., 2002b). In this chapter we use the new designation for this oligosaccharide structure. It has been demonstrated that CD176 is expressed on the surface of various cancer cells, such as breast carcinomas (Springer 1997; Imai et al., 2001; Goletz et al., 2003), colorectal carcinomas (Cao et al., 1995), hepatocellular carcinomas (HCC) (Cao et al., 1999), several leukaemias (Cao et al., 2008), and other types of cancer, but absent from almost all normal adult cell types (Cao et al., 1996). As a functional moiety, CD176 on the surface of cancer cells is involved in the invasive and metastatic properties of the cells (Cao et al., 1995). An anti-CD176 antibody could induce apoptosis of leukaemic cells (Cao et al., 2008). As CD176 is strongly expressed on the surface of cancer cells and virtually absent from normal tissues, it appears reasonable to assume that this carbohydrate structure is a suitable target for cancer biotherapy (Springer, 1997; Goletz et al., 2003; Franco, 2005).

In addition to its presence on tumour cells, CD176 is known as a differentiation antigen that is generally expressed in human foetal epithelia (Barr et al., 1989). We examined the co-

expression of these two markers of cancer-initiating cells, CD44 and CD133, with CD176 (Lin et al., 2010b). Double immunofluorescence staining experiments with lung, breast and liver cancer cell lines demonstrated that CD44 and CD176 were located at the cellular surface and exhibited co-expression of single cells or cell clusters (Figure 4). In the examined cancer tissues, cells co-expressing CD176 with CD44 and CD133 were also found. Furthermore, when we added 4-OHT to breast cancer cells (20 nM for 24 h), the $CD44^+/CD176^+$ phenotype in one of three cell lines (MDA-MB-435) was enhanced after this treatment. We consider this result as additional evidence for the assumption that this phenotype identifies cancer-initiating cells.

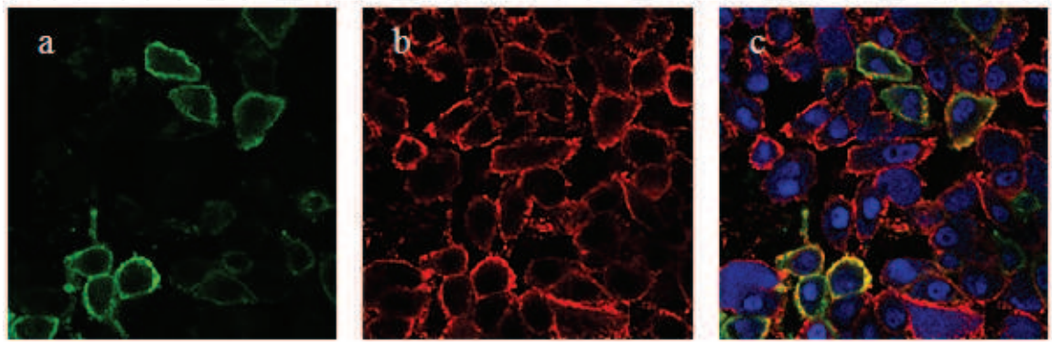


Fig. 4. Confocal microscopy analysis performed with the lung cancer cell line NCI-H446 (magnification: 400x). Cells were stained with monoclonal antibodies specific for CD44 (red) and CD176 (green). Nuclei were counterstained with DAPI (blue). CD44 is strongly expressed in most NCI-H446 cells (a). CD176 expression could be seen at the membrane of cell clusters (b). The mixed picture (c) demonstrates co-localization of CD44 and CD176 in these cell clusters (yellow) (from Lin et al., 2010b)

According to the cancer stem cell hypothesis, recurrences and metastases of cancer depend on cancer-initiating cells (Dalerba et al., 2007). The existence of a population of such cells with properties different from the tumour mass may explain why conventional therapies, e.g. treatment with tamoxifen, are only able to suppress cancer but often cannot completely eradicate it. On the contrary, this treatment may even enhance the number of cancer-initiating cells (Mani et al., 2008). On the other side, the elimination of cancer-initiating cells could actually prevent recrudescences of tumours. The development of new therapeutic approaches to target cancer-initiating cells may therefore have a profound impact on cancer therapy. Our current study demonstrated that CD176 is not only expressed on mature cancer cells but obviously also or even preferably on cancer-initiating cells of solid tumours. The identification of CD176 on cancer-initiating cells of solid tumours is an important argument for the development of CD176-based immunotherapies, and may explain the success of Georg Springer's early vaccination attempts (Springer, 1997). Demasking of CD176 seems to be a selective process that involves only a few among all possible candidate glycoproteins present at the cell membrane. The most prominent carrier molecule of CD176 identified in epithelial cells so far is the polymorphic epithelial mucin MUC-1, for example in breast and colorectal carcinoma (Barr et al., 1989; Cao et al., 1997; Baldus et al., 1998). In $CD34^+$ malignant human hematopoietic stem cells, we have observed that the major carrier of CD176 is a 150-kDa glycoprotein which is CD34 (Cao et al., 2008). Another study showed that a splice variant of CD44 is a carrier of CD176 on colorectal carcinomas (Singh et al.,

2001). In our study, we applied a special sandwich ELISA and examined whether CD44 might also be the carrier molecule for core-1 in lung, breast and liver carcinoma cells. Our data suggest that CD176 is indeed carried by CD44 in tumours other than colorectal carcinomas (Lin et al., 2010b). In other words, it is a more general phenomenon.

3. Conclusion

CD173 (Blood group antigen H type 2, H2), CD174 (Lewis Y, LeY) and CD176 (Thomsen-Friedenreich antigen, core-1) expression were observed in human lung, breast and liver carcinomas and in cell lines derived from these malignancies. Co-expression of CD173, CD174 and CD176 with CD44, as well as CD133 was found in vitro and in vivo. Evidence is provided through immunoprecipitation and in a new sandwich ELISA suggesting that CD44 is a carrier molecule for CD173, CD174 and CD176 not only in colorectal cancer as previously reported, but also in lung, breast and liver cancer. The identification of CD173, CD174, and CD176 on cancer-initiating cells may offer new opportunities in the design of therapies that target cancer-initiating cells in the prevention of relapse. More importantly, these data make CD176, which is almost absent on normal and benign adult human tissues, an even more promising target for tumour therapies.

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Cancer Stem Cells - The Cutting Edge

Edited by Prof. Stanley Shostak

ISBN 978-953-307-580-8
Hard cover, 606 pages
Publisher InTech
Published online 01, August, 2011
Published in print edition August, 2011

Over the last thirty years, the foremost inspiration for research on metastasis, cancer recurrence, and increased resistance to chemo- and radiotherapy has been the notion of cancer stem cells.The twenty-eight chapters assembled in Cancer Stem Cells - The Cutting Edge summarize the work of cancer researchers and oncologists at leading universities and hospitals around the world on every aspect of cancer stem cells, from theory and models to specific applications (glioma), from laboratory research on signal pathways to clinical trials of bio-therapies using a host of devices, from solutions to laboratory problems to speculation on cancersâ€™ stem cellsâ€™ evolution. Cancer stem cells may or may not be a subset of slowly dividing cancer cells that both disseminate cancers and defy oncotoxic drugs and radiation directed at rapidly dividing bulk cancer cells, but research on cancer stem cells has paid dividends for cancer prevention, detection, targeted treatment, and improved prognosis.

How to reference

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Wei-Ming Lin, Uwe Karsten, Steffen Goletz and Yi Cao (2011). Carbohydrate Antigens as Cancer-Initiating Cell Markers, Cancer Stem Cells - The Cutting Edge, Prof. Stanley Shostak (Ed.), ISBN: 978-953-307-580-8, InTech, Available from: http://www.intechopen.com/books/cancer-stem-cells-the-cutting-edge/carbohydrate-antigens-as-cancer-initiating-cell-markers

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