Human breast cancer cells share antigens with the myeloid monocyte lineage

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Summary We have examined the expression of several myeloid cell associated antigens, some of which are involved in myelomonocyte adhesion, in seven well characterized human breast cancer cell lines, since common properties of adheresness and migration are found in haemopoietic cells and epithelial cancer cells. Five of these cell lines were of metastatic origin and two were derived from primary breast carcinoma. Antigenic expression was evaluated by immunofluorescence (IF), flow cytometry (FCM), radioimmunoassay on live cells (RIA) and immunoperoxidase staining. None of these cell lines expressed T or B lymphoid specific antigens. Myeloid antigens My4, M01, and M0F11 (derived from the hybridization of mouse X63-Ag8 cells with spleen cells from Balb/c mice immunized with purified human monocytes) were expressed in the 7 cell lines. Leu M1, Leu M3, My9, and M02 antigens were expressed in some of the cell lines. Leu M2 and My7 antigens were not expressed or at very low levels. The expression of these myeloid antigens was also tested by immunoperoxidase staining, and found on frozen sections of normal mammary gland, fibroadenoma of the breast, primary breast cancer, and lymph node and skin metastases of breast tumours. This common expression in epithelial breast cells and in myeloid cells might be related to common biological functions such as interaction with extracellular matrix which precedes cell migration, a normal function of macrophages and an abnormal function expressed or amplified in human cancer epithelial cells.

Recent reports have described the expression of myelomonocyte associated antigens in small cell lung cancer cells (SCLC) (Ruff & Pert, 1984; Bunn et al., 1985; Ball et al., 1986; Gazdar et al., 1985) and advanced the hypothesis of a myeloid origin for this neoplasm (Ruff & Pert, 1984). Several facts contradicted this conclusion, since myeloid antigen expression was sometimes found in non SCLC lines (Bunn et al., 1985; Gazdar et al., 1985). Moreover certain leucocyte differentiation antigens such as those expressed on normal killer (NK) cells and those constituting the CD10 complex (CALLA) were more consistently expressed in SCLC and neuroectodermal cells (Bunn et al., 1985; Efreimis & Bekesi, 1986; Lipinski et al., 1983; Cole et al., 1985), and there are convincing biological data on the epithelial origin of SCLC (Cole et al., 1985).

Epithelial cells, either normal or malignant, interact with constituents of basement membranes (BM). This interaction in normal cells, leads to their differentiation. With metastatic cells, this interaction induces proteolysis of BM and dissemination. Such interactions with BM, proteolysis and migration behaviour are basic properties of polymorphonuclear (PMN) and macrophages. The antigenic commonality observed in SCLC cells and those of myeloid lineage could thus be related to the similar functional property of interaction with MB. In order to test this hypothesis, we have examined the expression of myeloid associated antigens in several well characterized human breast cancer cell lines and in biopsies of normal breast gland, benign breast tumors and malignant primary or metastatic breast carcinoma.

These myeloid antigens are not yet functionally characterized except two of them (Mo1 and Leu M1) which are involved in adhesive processes (Dana et al., 1983; Arnaout et al., 1985; Symington et al., 1986).

Materials and methods

Cell lines

Human breast carcinoma cell lines (HBCaCl) studied included MCF7 (Soule et al., 1973), MDA-MB231 (Cailleau et al., 1974), ZR75-1 (Engel et al., 1978), T47-D (Keydar et al., 1979) and H466B (Calvo et al., 1986) which were derived from metastatic breast carcinoma. Primary breast cancer lines were BT20 (Lasfargues & Ozzello, 1958) and H5573 (F. Calvo, unpublished). All cell lines were cultured in DMEM (Gibco) supplemented with 10% foetal bovine serum except H466B in DMEM/F12 supplemented with hormones and growth factors (Calvo et al., 1984) and 5% FBS. All these cell lines are of epithelial morphology and positively react with anti human milk fat globule membrane antibodies and anti epithelial cytokeratin antibodies.

Monoclonal antibodies (MoAb)

Anti My4 (IgG1, CD14), My7 (IgG1), My9 (IgG2b, CD33) from Coulter (Hialeah, Florida) recognize antigenic determinants on monocytes and acute myeloblastic leukaemias. Anti Leu M1 (IgM), Leu M2 (IgM), Leu M3 (IgG2b) were purchased from Becton Dickinson (Mountain View, California). Leu M1 (CD15) is a human myeloid antigen (lacto N fucopentaose III) present on PMN and circulating monocytes and was reported to be associated with adhesive functions. Leu M2 is a membrane antigen of monocytes, platelets and adherent macrophages. Leu M3 is a monocyte macrophage antigen. Anti M01 (IgM, CD11) and anti M02 (IgM, CD14) were from Coulter (Hialeah, Florida). M01 is found on adherent monocytes, PMN and NK cells and recognizes the C3b receptor which is involved in adhesion of these cells. M02 is found on adherent monocytes and blast cells from patients with myelomonocytic leukaemia.

MOF11 is a MoAb (IgG2b) derived from the hybridization of mouse X63-Ag8 cells with spleen cells from Balb/c mice immunized with purified human monocytes. It identifies a antigen present on monocytes, granulocytes and platelets and was a gift of Dr Poncelet (Sanofi, Montpellier, France). Anti T and anti B MoAb tested were kindly offered by Dr Bernard-Boumsell (Paris, France); they recognize antigens of the following differentiation clusters: CD1, CD2, CD3, CD5, CD7, CD8, CD10 (CALLA), and CD20 (B1), CD22 (B2), CD21 (B4), OKT9 (anti transferrin receptor MoAb) was purchased from Ortho-diagnostics (Raritan, NJ). Negative
control MoAbs included an antiviral (IgG) and anti-oxoplasma (IgM) and were gifts from Dr Rosetto (Paris).

**Indirect immunofluorescence microscopy and fluorocytometric analysis**

Cell suspensions from cell lines were incubated with saturating concentration of the monoclonal antibody (10^6 cells in 100 µl at 4°C for 30 min) washed twice, incubated with fluoresceinated goat anti mouse Ig of the appropriate class (Institut Pasteur, Paris, France) (1:50 dilution of 1 mg ml^-1 in 100 µl at 4°C for 30 min) washed twice, and analyzed for fluorescence using an inverted Zeiss fluorescence microscope and/or an Ortho 50 fluorometer (Ortho, California). For each cell line, samples were stained with a non reactive primary antibody of the same class and the secondary antibody, as negative control.

**Radioimmunooassay (RIA) on live cells**

In order to quantify the antigenic expression on the cell surface, a RIA on live cells was performed.

Briefly, cells were treated as above with the primary antibody and were incubated with a Fab' ^125^I iodinated sheep antibody to mouse IgG and IgM (Amer sham, France) (1/50 dilution of 1 mg ml^-1, 100 µl, at 4°C for 30 min), washed twice, and counted with a gamma counter (LKB Wallac, Turku, Finland). Nonspecific binding of negative controls was subtracted.

**Immunoperoxidase staining of cell lines and frozen sections of tissues**

Cell lines were cytocentrifuged (Shandon, London, England) onto glass slides and fixed in cold acetone (4°C). Frozen sections from normal breast biopsies, adenofibromas, breast cancers, metastatic breast cancer, and cyt centrifuged preparations were incubated with MoAb; immunoperoxidase staining was performed using the avidin-biotin peroxidase technique (Hsu et al., 1981) (Vectastain, ABC Kit, Vector Lab. Inc.) or a polyclonal antitumor immunoglobulin antibody conjugated to peroxidase (Dakopatt, Denmark). Controls were the same as above.

**Results**

**Indirect immunofluorescence of cell lines**

Expression of the various antigens studied in the 7 human breast cancer cell lines is shown in Table I.

Fluorescence was consistently negative with the antibodies recognizing B and T cell differentiation clusters. It was positive with anti OKT9 MoAb which recognizes the transferrin receptor. It was consistently positive with anti My4, M01, and MOF11 MoAb. Anti Leu M1, Leu M2, and M02 reacted diversely with the different cell lines tested. None of the 7 cell lines reacted with anti My7, anti My9 or expressed Leu M3 antigen.

**Radioimmunoassay on live cells**

In order to obtain greater sensitivity, to quantify antigenic determinants and to try to discriminate between antigenic expression on metastatic and primary breast cancer derived cell lines, a radioimmunoassay on live cells was performed.

Seven cell lines were examined for the binding of the anti My4, My7, My9, Leu M1, Leu M2, Leu M3, MO1, MO2 and MOF11 MoAbs.

As shown in Figure 1, all cell lines expressed antigenic determinants recognized by anti My4, MO1 and MOF11.

Significant binding of anti Leu M1 was observed with MCF-7 and HSL 53. Anti My9, MO2, and Leu M3 were significantly bound by MCF-7 and BT20 respectively. No obvious differences were observed between the five cell lines derived from breast cancer metastases (MCF-7, MDA-MB231, T47D, ZR75-1 and H466B) and the two cell lines established from primary breast cancer.

**Immunoperoxidase staining of cell lines and frozen tissue sections**

The immunoperoxidase staining patterns of malignant cell lines were similar to the immunofluorescence results, and a heterogeneous staining pattern was observed for each cell line (Figure 2A).

Analysis of the frozen tissue sections demonstrated that some of the myeloid-monocytes antigens were expressed on fresh human breast cells (Figure 2B, C, D; Table II). Anti My4, Leu M1, Leu M2 and MO1 stained non tumoral breast tissue and malignant breast tumours and the staining was heterogeneous. MOF11 positively stained malignant tissues while weak staining was observed in normal cells and no staining on non malignant tumour cells. Finally anti Leu M3 did not stain the tissue sections tested.

**Discussion**

Epithelial cells interact with BM constituents. From this interaction, normal cells retain their differentiation charac-

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Table I Immunofluorescence analysis of antibody reactivity with various cell lines of breast cancer origin. +: positive; --: negative staining; *: % of positively stained cells analyzed either by a cell sorter or by fluorescence microscopy; ND: not done.

| Monoclonal antibodies | MCF-7 | MDA-MB231 | T47-D | ZR75-1 | H466B | BT20 | HSL53 |
|-----------------------|-------|------------|-------|--------|-------|------|-------|
| Anti My4              | + (+24) | + (25)    | + (26) | + (30) | + (25) | + (32) | ND    |
| Anti My7              |       |           |       |        |       |      |       |
| Anti My9              |       |           |       |        |       |      |       |
| Anti Leu M1           | + (72) |           | + (12) | + (20) | + (38) | + (10) | + (54) |
| Anti Leu M2           |       |           |       |        |       |      |       |
| Anti Leu M3           |       |           |       |        |       |      |       |
| Anti MO1              |       |           |       |        |       |      |       |
| Anti MO2              |       |           |       |        |       |      |       |
| MOF11                 | + (45) | + (18)    | + (24) | + (22) | ND    | ND   | + (52) |
| Anti CD:              |       |           |       |        |       |      |       |
| 1-2-3                 |       |           |       |        |       |      |       |
| 5-7-8-10              |       |           |       |        |       |      |       |
| 19-20-21              |       |           |       |        |       |      |       |
| Anti OKT9             |       |           |       |        |       |      |       |
Common Antigens of Myelomonocytic and Breast Cancer Cells

Figure 1 Binding of monoclonal antibodies against myelomonocyte antigens to human breast cancer cell lines. Data are expressed as radioactivity bound (125I-labeled Fab2 anti mouse immunoglobulin) to primary antibody per 10⁶ cells.

![Graph showing binding of monoclonal antibodies to breast cancer cell lines](image)

- HSL53
- BT-20
- H466B
- ZR75-1
- T47 D
- MDA MB231
- MCF 7

Figure 2 Immunoperoxidase staining with anti myelomonocyte monoclonal antibodies. (A) Cytocentrifuged smears of MCF-7 cells stained with anti Leu M1 (× 250). (B) Frozen sections of skin metastasis of an adenocarcinoma of the breast stained with anti Leu M1. Ep: Epidermal cells; M: metastatic breast cancer cells (× 250). (C) Frozen section of a primitive breast adenocarcinoma stained with MOF11 (× 250). (D) Frozen section of normal breast tissue sample stained with anti My4 (× 250).
The present data clearly show that antigenic determinants present in the myeloid monocyte lineage are also present in breast cancer cell lines, and, to various degrees, in fresh sections of breast cancer and in non-malignant mammary gland. This expression of haemopoietic related antigens was restricted to the myelomonocytic lineage since neither T nor B differentiation antigens were expressed in the breast cancer cell lines tested. A common reactivity with these MoAbs implies that either common surface antigens or at least common epitopes are present in the different cell types tested.

It was recently reported that some antigenic determinants related to haemopoietic differentiation were expressed at the cell surface of small cell lung cancer (SCLC) (Ruff & Pert, 1984; Gazdar et al., 1985) and, to a lower extent, in epidermoid carcinoma (Bunn et al., 1985). Similarly, an NK cell antigen Leu 7, was expressed in SCLC and other neuroendocrine tumours such as pheochromocytoma and carcinoid tumours (Lipinski et al., 1983; Cole et al., 1985) but could not be detected on epithelial tumours like breast adenocarcinoma (Bunn et al., 1985). The Leu M1 antigen (lacto N fucopentaose III) has been shown to be present on human colon and lung cancer and renal tubule (Huang et al., 1983). The majority of the antigens reacting with the MoAbs raised against myelomonocytes have not yet been functionally characterized, and the biological significance of the antigenic commonality may be only speculative. However, some of these antigens have been associated with the adhesion properties of PMN and macrophages.

Such antigenic sharing between different cell types, is usually related to a common ontogeny. In fact, some of the antigens tested here are common to monocytes, macrophages, PMN and their putative precursors. In SCLC, a common ancestry with macrophages has been suggested by Ruff and Pert (1984). However, this hypothesis is controversial since SCLC seems to be of epithelial origin and some lung epidermoid and glandular carcinoma cell lines also share the same myeloid antigens (Bunn et al., 1985).

A second hypothesis implies the fusion of neoplastic cells with host macrophages which could account for the expression of macrophage differentiation associated antigens. There is suggestive evidence that such spontaneous fusions occur in vivo (Atkin, 1979; Kerbel et al., 1983; Larizza et al., 1984), and are associated with a highly malignant phenotype. However, in our study, no difference in binding was observed between primary or metastatic derived cell lines. Moreover, the staining of tissue sections with anti My4, Leu M1, Leu M2 and MO1 did not discriminate between normal, benign or primary and metastatic breast tissues. In contrast, MOF11, which stained non malignant tissues poorly, bound both primary and metastatic carcinoma cells strongly.

The third hypothesis implies that the antigenic commonality between myelomonocytes and epithelial cells reflects common cell functions such as interaction with BM. Indeed, normal and malignant epithelial cells and PMN and monocytes share the common biological property of interacting with basement membranes via several receptors and molecular interactions (Giavazzi et al., 1983; Yamada, 1983; Liotta, 1984; Hand et al., 1985; Charpin et al., 1986). Normal breast epithelial cells attach to their basement membrane constituted of collagen IV, laminin and glycosaminoglycans, and a permanent controlled proteolysis of this barrier is associated to its synthesis (Yamada, 1983; Hand et al., 1985; Charpin et al., 1986). These interactions lead to the differentiation and polarization of these cells (Gospodarowicz et al., 1978). Invasive tumours also attach to their matrix but the proteolytic process seems overexpressed and morphologically abnormal extracellular matrices are synthetized at the interface between stroma and tumour nodules (Charpin et al., 1986). Metastatic cells also interact with basement membrane, but its degradation predominates over synthesis (Liotta, 1984; Charpin et al., 1986; Thorgeirsson et al., 1985; Liotta et al., 1980; Terranova et al., 1986a). Phagocytes also adhere to constituents of basement membrane, have laminin like receptors (Huard et al., 1986), and laminin promotes their migratory ability (Wright & Gallin, 1979; Terranova et al., 1986b). Proteolytic activity and migration are secondary responses to adhesion (Liotta, 1984; Thorgeirsson et al., 1985; Terranova et al., 1986a; Wright & Gallin, 1979; Bano et al., 1986) and this expression varies from normal epithelium to invasive tumours, to metastatic cells and myelomonocytes. For instance, the CD11b receptor present at the surface of neutrophils and monocytes, is involved in adhesion (Arnaout et al., 1985) but plays a pleiomorphic role in the morphology, oriented mobility and proteolytic activity of these cells, as shown in the genetic deficiency of this glycoprotein family where adhesion, migration and proteolysis are abnormal (Dana et al., 1983). As far as our study is concerned, the expansion of antigens common to myeloid cells and cells of normal and transformed epithelia could mean that none of them is related to invasion but rather to the initial common step viz. interaction with BM.

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**Table II** Reactivity of antimyelomonocytes monoclonal antibodies with frozen sections of breast tissues (staining intensity is graded from + to ++ +).

| Tissues                  | My4 | Leu M1 | Leu M2 | Leu M3 | MO1 | MOF11 |
|-------------------------|-----|--------|--------|--------|-----|-------|
| Normal breast tissue    | ++  | ++     | ++     | -      | ++  | +     |
| Adenofibroma            | -   | ++++   | -      | ND     | +   | -     |
| Subcutaneous metastasis | ++  | ++++   | +      | -      | +++ | +     |
| Primary breast cancer   | ++  | ++++   | +++    | +      | +++ | +     |
| Lymph node metastasis   | +++ | +      | +++    | ND     | +   | +     |

Characteristics, and cancer cells respond by BM lysis and migration. Macrophages also interact with BM and this is the first event leading to migration.
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