Review

Should EMT of Cancer Cells Be Understood as Epithelial-Myeloid Transition?

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Abstract

Cancer cells express epithelial markers, and when progressing in malignancy they may express markers of the mesenchymal cell type. Therefore an epithelial-mesenchymal transition of the cancer cells is assumed. However the mesenchymal markers can equally well be interpreted as myeloid markers since they are common in both types of cell lineages. Moreover, cancer cells express multiple specific markers of the myeloid lineages thus giving rise to the hypothesis that the transition of cancer cells may be from epithelial to myeloid cells and not to mesenchymal cells. This interpretation would better explain why cancer cells, often already in their primary cancer site, frequently show properties common to those of macrophages, platelets and pre-/osteoclasts.

Key words: Epithelial-mesenchymal transition, epithelial-myeloid transition, osteomimetic properties of cancer cells; macrophage and platelet traits of cancer cells, common clusters of differentiation between cancer cells and cells of the myeloid lineage

Introduction

The epithelial-mesenchymal transition (EMT) of cancer cells is assumed to be a process that causes a functional and phenotypical transition of polarised epithelial cells into the migratory extracellular matrix producing mesenchymal cells. In order to acquire a mesenchymal migratory phenotype (motility and invasiveness), cancer cells must shed many of their epithelial characteristics, detach from the epithelial sheet and undergo a drastic alteration. It appears therefore that EMT is a key developmental programme often activated during cancer invasion and metastasis [1, 2].

This hypothesis is based on the fact that key mesenchymal markers, such as vimentin, fibronectin, N-Cadherin, alphavbeta3-integrins and FSP-1, can be detected in a subset of cancer cells. The EMT seems to pathologically recapitulate the normal epithelial-mesenchymal transition occurring during mammalian development, and is thought to be to some extent comparable to the EMT during physiological wound healing [3]. However, there is some incongruity in this hypothesis, as it cannot explain why cancer cells with mesenchymal markers show many specifically phenotypical and functional traits of monocytes, macrophages, platelets and pre-/osteoclasts, i.e. traits of the myeloid lineage cells [4-11].

The key mesenchymal markers are not specific to mesenchymal cells, but can also be found in cells of the hematopoietic lineage, and especially in the myeloid lineage. [12] We therefore raise the question whether the transition of cancer cells can be interpreted as an epithelial-myeloid transition. This would explain the peculiar properties of cancer not in accord with their assumed mesenchymal character, which have therefore so far been interpreted as a kind of mimicry of properties of the myeloid lineage cells.

Osteomimetic properties of cancer cells

Multiple publications describe the osteomimetic properties of cancer cells and relate this to their bone metastasizing tendency [13-18]. Most known human
carcinomas show an increased expression of bone-specific proteins, i.e. osteopontin, osteocalcin and sialoprotein [16]. The expression of bone-specific proteins by primary tumour cells is not restricted to cancer cells metastasizing to bone, but is a general feature of the malignant phenotype. Moreover cancer cells in the primary tumour site express various enzymes commonly expressed by osteoclasts as well, such as MMP-9, TRAP, Cathepsin-K, carbonic anhydrase and the vacuolic H+-ATPase [19-21]. These features do not comply with the assumed epithelial character or mixed epithelial-mesenchymal character of cancer cells in the primary or metastatic site. Cancer cells are usually thought to originate in the epithelium from epithelial cells, and the question arises how cancer cells of epithelial origin can adopt osteometric properties.

**More preosteoclastic traits of cancer cells**

The functional properties of cancer cells also reflect specifically preosteoclastic behaviour. These are: matrix-resolving properties, hormone and neuronal dependence, coupling with mesenchymal cells, migrating and transmigrating properties, neurogenetic properties, trafficking to the bone, immune competence, sensitivity to antirheumatics, bisphosphonates, polyphenols and steroids [7]. Most of these characteristics do not comply with the behaviour of mesenchymal cells. Immune competence is a decisive trait of cells of the myeloid lineage and is uncharacteristic of matured mesenchymal cells. The immune competence of the cancer cells is however one decisive hallmark of cancer cells. It contributes to their malignancy and therapy resistance as it can deviate all immune strategies, avoiding repulsion or elimination of the tumour. Another characteristic trait of pre-/osteoclasts is their coupling with mesenchymal cells, i.e. with osteoblasts. The development of pre-osteoclasts depends on their interaction with osteoblasts. It has been well demonstrated that cancer cells need co-conspirators for their development such as tumour-associated fibroblasts, i.e. cells of the mesenchymal lineage. Cancer cells depend for their progression on coupling with mesenchymal cells i.e. the tumour-associated fibroblasts, in the same way that pre-/osteoclasts depend on osteoblasts for their differentiation.

When preosteoclasts fuse into an osteoclast they intracellularly overexpress certain signalling pathways which are likewise overexpressed in cancer cells during their proliferation [22].

**Common clusters of differentiation between cancer cells and cells of the myeloid lineage**

Comparing the surface markers of cancer cells with those of osteoclasts and their myeloid lineage progenitors, we detect multiple correspondences. The following clusters of differentiation commonly expressed by myeloid cells including pre- and osteoclast cells are surface markers of various cancer cells as well: CD9 - CD11b, CD13 - CD15, CD18, CD20, CD24, CD26, CD30, CD31, CD36, CD38, CD40, CD 41, CD43 - CD 47, CD49, CD51, CD53 - CD56, CD58, CD59, CD61, CD63, CD68, CD70, CD71, CD73, CD80/86, CD81, CD82, CD86, CD87, CD90, CD95, CD97, CD98, CD 105, CD106, CD112, CD115, CD117, CD124, CD133, CD137, CD146, CD147 CD151, CD155, CD163, CD164, CD166, CD171, CD184, CD200, CD227, CD274 and CD326 (for references see table 1).

We can conclude from the clusters of differentiation that various stages of myeloid lineage, from stem cells to mature cells, can be detected in cancer cell lines and in cancer tumours. As far as we are aware, many of these clusters of differentiation have not so far been detected on mesenchymal cells as CD10, CD11, CD14, CD18, CD20, CD45 and others – see table 1.

**Table 1:** Common clusters of differentiation among epithelial, cancer, mesenchymal and myeloid cells. In the lines of epithelial and mesenchymal cells, account is taken of the indications published in: Charles Janeway et al.: The Immune System in Health and Disease, Taylor and Francis Books Inc. New York 2001 (5th edition).

| Clusters of differentiation | Cells of myeloid origin | Cancer cells | Epithelial cells | Mesenchymal cells | References |
|-----------------------------|-------------------------|--------------|-----------------|------------------|------------|
| CD9                         | +                       | +            | +               | +                | [36 - 40]  |
| CD10                        | +                       | +            | -               | -                | [41 - 43]  |
| CD11a,b (CD11b= Mac-1; CD11a/ CD18=LFA-1) | +       | +            | -               | -                | [44, 40]   |
| CD13                        | +                       | +            | -               | +                | [40, 45]   |
| CD14                        | +                       | +            | -               | -                | [40, 44, 46] |
| CD15 (Lewis X)              | +                       | +            | -               | +                | [47, 48]   |
| CD18                        | +                       | +            | -               | -                | [40, 49]   |
| CD20                        | +                       | +            | -               | -                | [50, 51]   |
| CD24                        | +                       | +            | -               | +                | [52 - 54]  |
| CD26 (Mannose receptor) | + | + | - | - | [6, 43] |
| CD30 | + | + | - | - | [55, 56] |
| CD31 (PECAM-1) | + | + | - | + | [57] |
| CD36 (Fatty acid transporter, TSP receptor) | + | + | + | + | [58 - 60] |
| CD38 | + | + | - | - | [50, 61, 62] |
| CD40 | + | + | - | - | [40, 63, 64] |
| CD41 | + | + | - | - | [65 - 67] |
| CD43 | + | + | - | - | [68] |
| CD44 | + | + | + | + | [69] |
| CD45 | + | + | - | - | [40, 48, 55] |
| CD46 (membrane cofactor protein MCP) | + | + | - | - | [70, 71] |
| CD47 (Thrombospondin-1 receptor) | + | + | + | + | [72, 73] |
| CD49 | + | + | + | + | [43, 74] |
| CD51 Alpha V; CD51/CD61: Vitronectin Receptor (integrin alphaVbeta3) | + | + | + | + | [75] |
| CD53 | + | + | + | - | [40, 76] |
| CD54 (Icam-1) | + | + | + | + | [40, 43, 48, 72] |
| CD55 (DAF) | + | + | + | + | [70, 71] |
| CD56 | + | + | - | - | [70, 77, 78] |
| CD58 | + | + | + | + | [40, 72] |
| CD59 | + | + | + | + | [71, 79] |
| CD61 (beta3 integrin) | + | + | - | - | [80, 81] |
| CD63 | + | + | + | - | [40, 70, 82] |
| CD68 (KP1) | + | + | - | + | [40, 48, 83, 84] |
| CD70 | + | + | - | - | [85, 86] |
| CD71 (Transferrin receptor) | + | + | + | + | [48, 87] |
| CD73 | + | + | + | + | [87 - 89] |
| CD80/86 (B7) | + | + | - | - | [40, 90, 91] |
| CD81 | + | + | - | - | [87, 92] |
| CD82 | + | + | + | - | [92, 39] |
| CD86 | + | + | - | - | [40, 91, 93] |
| CD87 (Urokinase plasminogen activator receptors = uPAR) | + | + | + | + | [40, 94, 95] |
| CD90 | + | + | - | + | [46, 96, 97] |
| CD95 (FasR) | + | + | - | - | [50, 98] |
| CD97 | + | + | - | - | [87, 99] |
| CD98 | + | + | - | - | [100, 101] |
| CD105 | + | + | - | + | [43, 102, 103] |
| CD106 (VICAM-1) | + | + | + | - | [40, 104] |
| CD112 (Nectin-2) | + | + | + | + | [105 - 107] |
| CD115 (c-FMS) | + | + | + | + | [108, 109] |
| CD117 (c-Kit) | + | + | - | + | [110, 111] |
| CD124 (Interleukin-4 Receptor) | + | + | - | - | [112, 113] |
| CD133 | + | + | + | - | [114 - 116] |
| CD137 | + | + | - | - | [117, 118] |
| CD146 | + | + | - | + | [119 - 122] |
| CD147 (Basigin, Emmprin = Extra-cellular matrix metallo-proteinase inducer) | + | + | + | + | [40, 123] |
| CD151 | + | + | + | + | [87, 92] |
| CD155 | + | + | + | - | [40, 124] |
| CD163 | + | + | - | - | [8, 40, 125] |
| CD164 | + | + | + | - | [43, 126, 127] |
| CD166 (ALCAM) | + | + | + | - | [128, 129] |
| CD171 (L1CAM) | + | + | + | - | [40, 130] |
| CD184 (CXCR4) | + | + | - | - | [43, 131] |
| CD200 | + | + | - | - | [40, 132] |
| CD227 (Mucin1) | + | + | + | - | [25, 43, 133] |
| CD274 (CPD-L1, B7-H1, Programmed death ligand 1) | + | + | - | - | [134, 135] |
| CD326 (Epcam) | + | + | + | - | [24 - 136] |
Other common surface markers

Other than the above cited clusters of differentiation, there are a multiplicity of surface markers expressed by both cancer and myeloid lineage cells, of which we will name only the following: TLRs, RANK, ADAM, DAP12, OSCAR, MAC387, NK1 receptor, BMP receptor, Protease activated receptor-1, TRAF-6 and calcitonin receptor. The calcitonin receptor and TRAP are specific osteoclast markers [23]. These cell markers are neither expressed by epithelial cells nor by mesenchymal cells. This demonstrates that cancer cells, even in their primary site, are more related to the various stages of myeloid cells, i.e. passing from stem cells to progenitor cells of monocytes, dendritic cells, macrophages through to osteoclasts. Thus we can question the mesenchymal character of cancer cells undergoing the hypothesized EMT.

Epithelial markers of cancer cells

Cancer cells are thought to be of epithelial origin due to their epithelial markers. But certain cells of the myeloid lineage, the Langerhans cells, usually adopt some epithelial markers as well. Langerhans cells show a high degree of epithelial surface markers CD326 (EpCAM) [24], CD227 (Mucin1) [25], and E-Cadherin [26] in the epidermis, thereby connecting them with keratinocytes. Whether they may also adopt a local cytoheratin scaffold has so far not been described to our knowledge. In connection with these epithelial markers of the myeloid lineage cells, it is noteworthy that haematopoietic lineage-committed bone marrow cells and not cloned cultures of mesenchymal cells contribute to the regeneration of renal tubular epithelium after HgCl2-induced acute tubular injury [27]. It seems that the hematopoietic stem cells transdifferentiate into renal tubular epithelial cells or at least become incorporated appropriately into renal tubular epithelium after acute renal tubular damage. The transdifferentiation of haematological stem cell into epithelial cells may be due to cell fusion [27, 28].

Are epithelial cells required for carcinogenesis?

We not only question the epithelial-mesenchymal transition, but also the purely epithelial origin of cancer cells. MTA transgenic mice are further evidence that epithelial cells alone cannot induce carcinogenesis in the skin. Cells of the myeloid lineage, like Langerhans cells in the epidermis, are required for carcinogenesis. Researchers expected MTA transgenic mice to be very prone to skin carcinogenesis due to the lack of Langerhans cells in their epidermis. The contrary was the case. The animals are resistant to squamous cell carcinoma induction in the skin [29, 30]. This fact can be explained by the hypothesis that cells of myeloid origin, and not epithelial cells alone, are a prerequisite for carcinogenesis.

The MTA transgenic mice are deficient in MHC-II positive cells in the epidermis and therefore Langerhans cells or any other myeloid cells are completely absent in the epidermis [31]. The fraction of MHC-II cells in the epidermis represent dendritic/Langerhans cells which still retain sufficient plasticity and consequently the potential to transdifferentiate into pre-/osteoclasts. Various in-vitro and in-vivo studies demonstrate this transdifferentiation of dendritic cells, e.g. in a rheumatoid arthritis microenvironment [32]. We can assume that this plasticity applies to the Langerhans cell as a subset of dendritic cells too.

Origin of cancer cells, and progenitor cells

The myeloid characteristics of cancer cells may lead us to ask whether these cells are really of epithelial origin or rather, at least in part, of myeloid origin. In the steady state of the epidermis, the Langerhans cells multiply in the skin and remain there for many years without being replaced by circulating monocytes. In the case of oxidative stress induced for example by UV irradiation or chemically by DMBA-TPA application, the resident Langerhans cells are depleted and replaced by circulating bone marrow-derived monocytes, which differentiate into Langerhans cells in the epidermis. If the oxidative stress continues over a longer period, a microenvironment arises in the epidermis that is characterized by the activity of M-CSF, RANKL, and hypoxia signalling [29]. This network may direct the MHC-II positive cells to transdifferentiate in the direction of pre-/osteoclasts, since the same environment governs the fusing of certain monocytes at the bone site during their differentiation into osteoclasts. Other still unknown factors may play a role in this process. The preosteoclasts derived from dendritic cells, surprisingly, are more prone to fuse than preosteoclasts directly derived from the bone marrow monocyte [32]. We hypothesise that under the described circumstances these cells fuse with keratinocyte or melanocyte progenitors expressing the fusion marker CD98 in the basal cell layer. As this fusion occurs via inadequate partners, it may result in aneuploidy and the merged characteristics of myeloid cells with keratinocytes or melanocytes, which are specific features of cancer cells. These cells have thus activated all the signalling pathways normally activated when monocytes/preosteoclasts fuse into osteoclasts at bone sites [22].
Where carcinogenesis is absent

We have described the MTA mice where carcinogenesis cannot be induced due to the lack of MHC II positive cells in the epidermis. A comparable situation has been described for the inner ear, which likewise seems resistant to carcinogenesis [33]. So far no primary cancer has been detected and described in the inner ear even in the case of chronic inflammation. This may be due to inhibition of differentiation of monocytes and Langerhans cells into osteoclasts, in this case caused by extremely high levels of osteoprotegerin and reduced expression of M-CSF and IGF-1.

A third example is the naked mole rat which does not develop cancer. There are various hypotheses for the lack of carcinogenesis in these animals, but none seems to be conclusive so far [34, 35].

Conclusions

On the basis of phenotypical features, functional characteristics and specific intracellular signalling activities, we hypothesise that cancer cells at least partly originate from the myeloid lineage. Cancer cells can be seen in different stages of the myeloid lineage passing - with the additional feature of malignancy - from bone marrow stem cells via monocytes through to pre- and osteoclasts. We can conclude that the osteomimetic properties of cancer cells are inherent properties of these cells and consequently cannot be interpreted as hoaxed and opportunistic features of mesenchymal cancer cells arising only for metastasis purposes in the bone. It is uncertain as yet whether the fusogenic properties of macrophages and preosteoclasts or their plasticity allow them to adopt local cytokeratin characteristics, and how these aspects may be connected with their malignancy. This is an issue for further research.

Based on these findings, the hypothesis of an epithelial-mesenchymal transition of cancers in their progression to metastasis must be severely questioned. The markers interpreted as mesenchymal markers of cancers cell can be judged as myeloid markers as well because they are common to both types of cells. Based on the phenotypical features and their functional properties in cancer, we propose another transition hypothesis. In a transition such as the phenotypical change in cancer cells apparent during their malignancy progression, an epithelial-myeloid transition would better explain the various features of the cancer’s malignancy.

Table 2: Common highly expressed markers shared by cancer and myeloid cells with high specificity for these cells.

| Markers                                      | Monocyte and pre-/osteoclast markers | Cancer cells                                           | Expression in other cells                      | References               |
|----------------------------------------------|-------------------------------------|------------------------------------------------------|-----------------------------------------------|--------------------------|
| TRAP                                         | Osteoclasts, activated macrophages  | Breast, ovary, cervix, melanoma                      | Neurons                                       | [21, 137, 138]           |
| RANK                                         | Preosteoclast                        | Breast, melanoma, prostate, colo-rectal, kidney, lung, head and neck, liver | Epithelial cells in mammary gland during pregnancy | [19, 139]               |
| Cathepsin K                                  | Osteoclasts, macrophages            | Breast, lung, prostate                               | Inflammatory dermal fibroblasts               | [19, 140]               |
| MMP-9, MMP-2                                 | Osteoclasts, macrophages            | Prostate, breast, glioma, head and neck, colorectum, bladder, lung | Connective tissue and inflammatory fibroblasts | [19]                    |
| Calcitonin receptor                          | Osteoclasts                         | Glioblastoma, prostate, breast                      | -                                             | [19]                    |
| DAP12                                        | Pre-/osteoclasts, dendritic cells   | Breast, prostate                                    | Neurons                                       | [19, 143]               |
| BMP receptor (Bone morphogenetic protein receptor) | Preosteoclasts                                      | Breast, prostate                                    | Stomach and peritoneal lining, CAF           | [20, 144]               |
| Carbonic anhydrase 2 and 12                  | Osteoclasts                         | Kidney, lung, head and neck, glioma, breast         | Osteoblasts, mammary gland during lactation, kidney epithelial cells | [145 - 148]           |
| PTHrP, PTH1R                                 | Preosteoclasts, osteoclasts         | Breast, lung, head and neck, prostate, kidney, colorectum | Epithelial cells                             | [149]                   |
| TLR4                                         | Osteoclasts, Macrophages            | Colon, lung and head neck, SCC of oesophagus, melanoma | Tumor stroma                                  | [150 - 152]           |
| ADAM12 / HER2                                | Pre-/osteoclasts, monocytes, dendritic cells | Breast, head and neck                               | Angiogenesis; spatio-temporal regulation     | [153, 154]           |

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Competing Interests

The authors have declared that no competing interest exists.

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