



PERSPECTIVES

Epithelial-mesenchymal transition as strategic microenvironment mimicry for cancer cell survival and immune escape?



Available online 5 November 2016

KEYWORDS

Cancer;
EMT;
Immune escape;
Mimicry

Abstract Epithelial-mesenchymal transition (EMT) is the phenotypic transition of epithelial cells to mesenchymal cells characterized by loss of epithelial markers, loss of intercellular adherence and acquirement of mesenchymal cell markers and increased locomotive ability. EMT is widely considered to be a gene regulated process necessary for cancer metastasis. Yet it is a highly controversial issue. We here propose that EMT is an environmentally induced cell behavior. It is the mimicry of their living environment. It is a survival strategy, a way of immune escape. We also propose here that the epithelial cell markers may functionally act as tumor antigens since in the mesenchymal surroundings there are no other structures bearing the same antigens as epithelial cells.

Copyright © 2016, Chongqing Medical University. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Epithelial-mesenchymal transition (EMT), originally a term in embryology describing the process of mesoderm formation and extension from the epithelial ectoderm, has been a hot spot of cancer research for its supposed roles in the process of cancer progression and metastasis for the past decade. There are a few hallmarks of EMT, including loss of epithelial cell polarity, loss expression of epithelial cell membrane markers such as E-cadherin and p120-catenin, and the acquired expression of mesenchymal cell marker vimentin. This phenotypical change of epithelial carcinoma cells is widely considered to be an essential step for cancer metastasis. However, there remains a fierce disagreement

on the genuine existence and the role of EMT, and its role in cancer metastasis.¹ We here propose a new explanation for the role of EMT, by focusing its biological significance in cancer cell survival.

Controversies

Although publications on the role of EMT in cancer metastasis have been increasing rapidly, there exist intense debates on the existence of EMT and the supposed role of EMT in cancer metastasis.¹ At first, some pathologists doubt the real existence of EMT.^{1–3} The pathological picture of EMT somewhat depends on who is to explain it. Serious pathologist like Dr. Tarin of California University denied the concept of EMT, even in the embryonic development.² The second aspect of the controversies is the paradoxes of EMT phenomena with clinical outcomes.

Peer review under responsibility of Chongqing Medical University.

<http://dx.doi.org/10.1016/j.gendis.2016.10.001>

2352-3042/Copyright © 2016, Chongqing Medical University. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

In the breast pathology, there is a lesion termed lobular tumor, which includes lobular carcinoma in situ (LCIS), and invasive lobular carcinoma (ILC). Both the lesions are characterized by the loss of E-cadherin expression, and the loose connection between the tumor cells. However, when simple LCIS is pathologically diagnosed, clinicians would not take treatment procedures if no further signs of malignancies were found.⁴ Clinical studies have long established that most LCIS did not develop further.⁴ This fact clearly does not support the notion of in situ carcinoma cells first go through EMT, then degrade the basement membrane by secreting matrix metalloproteinase (MMP), and evolve to invasive carcinoma.⁵ Moreover, in spite of negative E-cadherin expression, the invasive lobular carcinoma of breast do not show a worse clinical outcome as comparing with the invasive ductal carcinoma, which is the most popular histological type of breast cancer and retains E-cadherin expression. Indeed, the signet ring cell gastric cancer is without E-cadherin expression, and extremely poor clinical outcomes.⁶ For the reverse, Chu et al found that in invasive breast cancer the overexpression of E-cadherin is associated with decreased relapse-free survival.⁷ At a big vision, the level of E-cadherin expression has not been found to be clinically significant for the prognosis of cancer patients in most types of cancer.

Paradoxes of EMT also extend to cultured cell lines. A highly metastatic mouse breast cancer cell line, 4T1, has a high level of E-cadherin expression.⁷ In our experience, these cells adhere very tightly with each other, and to the culture plate. They are very difficult to digest, hard to disperse by enzyme or by pipetting. Therefore, intercellular tight connection is not a barrier to metastasis. In other words, EMT is not essential for metastasis. Notably, a recent study published in *Nature* clearly showed that EMT was not required for lung metastasis of breast cancer, but contributed to chemoresistance.⁸

More evidence come from the fact that desmoglein 3, one of the desmosomal cadherins which mediate cell–cell adhesion in desmosome, has an increased expression in a variety of cancers.⁹ This fact also contradicts the notion of EMT in cancer metastasis.

New vision on the biology of EMT

We here suggest a novel biological role of EMT in cancer. To understand EMT, we need to compare the living environment of normal epithelial cells with that of the invasive cancer cells, which is by nature epithelial cells. The normal epithelium is separated from the mesenchymal tissue by a thin, yet very important structure, the basement membrane. As a result, the normal epithelial cells are in a special environment in which there are no blood vessels or lymphatics. While the carcinoma cells are epithelial cells in mesenchyme without protection of intact basement membrane. They are cells displaced to the wrong mesenchymal territory.⁵ A critical question which perplexes immunologists is that if the epithelial cells were put into the mesenchymal tissue, would immunoreactions be provoked?

The immediate response of immunologists to this question would be no. But soon he/she would admit that there is no answer to it yet. By the clonal selection theory of Burnet, all the lymphocyte clones which respond to self-

antigens were all eliminated during the embryonic development.¹⁰ However, by logic we cannot refute a reasonable hypothesis by an established theory, because any theory in nature is hypothesis with uncertainty. In fact, the clonal selection theory has been facing serious challenges for many years.¹¹ For example, if all the self-recognizing lymphocyte clones were eliminated, how did the self-antibodies were produced in patients with autoimmune diseases?¹²

Another paradoxical question is the identity of tumor antigen. So far there are no tumor specific antigens identified for most types of cancer. Yet undoubtedly, the organism exerts immune reaction against cancer. This raise the question of what antigens are these immune reactions targeting at?

Now we come back to the invasive cancer. By nature, the invasive cancer cells are epithelial cells dispersed in mesenchymal tissue. There is no surrounding basement membrane to protect them. They are facing the immune cells directly. In parable, the normal epithelium is zoo, or city, while the mesenchymal microenvironment is jungle. They are facing a variety of stresses,¹³ of which one is immune stress. They have to find ways to increase their survival chances. It will be helpful to take a look at what those creatures do in the jungle.

A universal phenotypic behavior of all the creatures is not to stand out from the surroundings, but to keep as closely similar as possible to their surroundings. The term for this phenomena is mimicry, or camouflage. The pepper moth and grass hoppers wear different colors and graphic patterns in different surroundings. That makes them less vulnerable to the predators. The polar bears are white because it gives them more chance to successively hunt.

Now here is the case of cancer cells with epithelial markers in the mesenchymal tissue. Obviously they are invaders in a surrounding of no other structures which bear epithelial markers. These invaders are to bring damage to the organism. They constitute danger.¹⁴ By the danger model of immune reaction proposed by Matzinger,¹⁵ the immune cells will try to destroy these invading epithelial cells.^{14,15} Whatever the reason is, the immune system needs to eliminate the invaded epithelial cells to keep the normal structure of the body. Their target could be nothing but the epithelial markers on the cell membrane of these cancer cells, if there were no new antigens emerge from gene mutations.

Then a natural choice for the cancer cells is to lower the level of epithelial cell marker expression, such as that of E-cadherin. This would be especially the strategy for those of the dispersed single, or small clusters of cancer cells, and those at the periphery of cancer tissue. Interestingly, this corresponds to the hallmark of EMT. Therefore, EMT is a strategy of immune escape adopted by cancer cells to increase their chances of survival in mesenchymal tissues, by mimicry. Alternatively, the misplaced epithelial cells may really transform to mesenchymal cells. They not only lose the expression of epithelial markers, but also acquire the expression of vimentin, a mesenchymal cell marker, and morphologically take the shape of mesenchymal cells. In such a case, it would be hard to identify them, not only by immune cells, but also by pathologists, by cancer scientists.

This type of genuine EMT may account for the mutations seen in cancer stromal cells.¹⁶

However, for a large cancer mass, lowering the epithelial marker expression is not the only way of protecting themselves. The cancer cells would strengthen their intercellular connections to prevent infiltration of immune cells.⁹ In analogy, when an army was in action, it would take effective measures to strengthen their connection to prevent infiltration attempts from the enemy. Otherwise it would be a disaster. Therefore, the decreased expression of epithelial markers in dispersed cancer cells and the strengthened intercellular connection characterized by up-regulation of desmoglein proteins are both survival strategies of cancer cells.

Conclusion

Carcinoma cells are epithelial cells malignantly transformed in the wrong, mesenchymal microenvironment. Their epithelial markers make them stand out from the mesenchymal surroundings and easily become the targets of immune cells. Consequently, the cancer cells take the strategy of mimicry to lower its identity by simulation of their surroundings, which is a practical approach of immune escape. Therefore, EMT is a basic survival strategy adopted by cancer cells in the stressful environment. Although metastasis is also a stress response of cancer cells,^{13,17} EMT may not be an essential process for cancer metastasis.⁸ An important issue raised in this paper is the identity of cancer antigens and the possibility of epithelial cell markers as working antigen in cancer immunity. Elucidation of this basic question will help understanding the biology of cancer and the role of immunity in cancer progression, which is a typical double-edged sword. By one of the edge, immunity checks the development of cancer by killing cancer cells; by the other edge, immunity facilitates cancer progression by inflammation. Interestingly, the paradoxical, these opposite effects of immunity in cancer are widely accepted by cancer researchers, which is a so-called antinomy by Immanuel Kant.

Declaration of conflicts of interest

None.

Acknowledgement

This study was supported by grant of NSFC No. 30971535 and State Key Lab of Cancer Biology Grant (To RA Wang).

References

- Ledford H. Cancer theory faces doubts. *Nature*. 2011; 472(7343):273.
- Tarin D, Thompson EW, Newgreen DF. The fallacy of epithelial mesenchymal transition in neoplasia. *Cancer Res*. 2005;65(14): 5996–6000. discussion 6000–1.
- Thompson EW, Newgreen DF, Tarin D. Carcinoma invasion and metastasis: a role for epithelial-mesenchymal transition? *Cancer Res*. 2005;65(14):5991–5995. discussion 5995.
- Frykberg ER. Lobular carcinoma in situ of the breast. *Breast J*. 1999;5(5):296–303.
- Wang RA, Li ZS, Zhang HZ, et al. Invasive cancers are not necessarily from preformed in situ tumours – an alternative way of carcinogenesis from misplaced stem cells. *J Cell Mol Med*. 2013;17(7):921–926.
- van Roy F. Beyond E-cadherin: roles of other cadherin superfamily members in cancer. *Nat Rev Cancer*. 2014;14(2): 121–134.
- Chu K, Boley KM, Moraes R, et al. The paradox of E-cadherin: role in response to hypoxia in the tumor microenvironment and regulation of energy metabolism. *Oncotarget*. 2013;4(3): 446–462.
- Fischer KR, Durrans A, Lee S, et al. Epithelial-to-mesenchymal transition is not required for lung metastasis but contributes to chemoresistance. *Nature*. 2015;527(7579):472–476.
- Brown L, Wan H. Desmoglein 3: a help or a hindrance in cancer progression? *Cancers (Basel)*. 2015;7(1):266–286.
- Mackay IR, Larkin L, Burnet FM. Failure of autoimmune antibody to react with antigen prepared from the individual's own tissues. *Lancet*. 1957;273(6986):122–123.
- Cohen IR. The cognitive principle challenges clonal selection. *Immunol Today*. 1992;13(11):441–444.
- Cohen IR. Autoimmunity shifts paradigms. *Isr J Med Sci*. 1994; 30(3):37–378.
- Wang RA, Lu YY, Fan DM. Reasons for cancer metastasis: a holistic perspective. *Mol Clin Oncol*. 2015;3:1199–1202.
- Fuchs EJ, Matzinger P. Is cancer dangerous to the immune system? *Semin Immunol*. 1996;8(5):271–280.
- Matzinger P. The danger model: a renewed sense of self. *Science*. 2002;296(5566):301–305.
- Patocs A, Zhang L, Xu Y, et al. Breast-cancer stromal cells with TP53 mutations and nodal metastases. *N Engl J Med*. 2007; 357(25):2543–2551.
- Wang RA. MTA1-a stress response protein: a master regulator of gene expression and cancer cell behavior. *Cancer Metastasis Rev*. 2014;33(4):1001–1009.

Jun-Hui Qin
Li Wang
Qin-Long Li
Yuan Liang
Zhen-Yu Ke
Rui-An Wang*

State Key Laboratory of Cancer Biology, Xijing Hospital,
The Fourth Military Medical University,
Xi'an, Shaanxi 710032, China

Department of Pathology, Xijing Hospital,
The Fourth Military Medical University,
Xi'an, Shaanxi 710032, China

*Corresponding author. Department of Pathology,
The Fourth Military Medical University,
Xi'an, 710032, China. Fax: +86 29 84779175.
E-mail address: wangra@fmmu.edu.cn (R.-A. Wang)

30 August 2016