Cancer Cell Research 21 (2019) 529-535

Available at http:// www.cancercellresearch.org ISSN 2161-2609

The function of phenotypic plasticity in tumor cells

Jie Yu[1], Fen Yu[2], Lin Shi[2], Nianrong Luo[3], Yongxia Chen[4], Xia Liu[2], Yongfeng Jia[2*]

[1]Department of Pathology, the Fourth Hospital of Jinan, Jinan, 250031, China

[2]Department of Pathology, the First Affiliated Hospital of Inner Mongolia Medical University, Huhhot, 010059, China

[3]Physical examination center, the Inner Mongolia Autonomous Region people's Hospital, Huhhot, 010017, China

[4]Tumor Molecular Diagnostic Laboratory, People's Affiliated Hospital of Inner Mongolia Medical University, Hohhot, 010020, China

Abstract: **Tumor is an increasingly common disease in today's society, it is also one of the major serious diseases do harm to human beings. But people still know little about how tumor cells work after lots of efforts were put to understand them. There is one primarily interrelated theme found on a combination of clinical and experimental observations of phenotypic plasticity. Changes of phenotypic plasticity might be induced by Epithelial-mesenchymal transition (EMT), cancer stem cells (CSCs), and vasculogenic mimicry (VM), or they interacted together, at least partly. Although they have important impacts on tumor biology, the clinical relevance of these concepts remains to be recapitulated. In this review, we will update the current state of correlations between EMT, CSCs, and VM formation with a focus on their contributions to phenotypic plasticity, their clinical implications for the design of therapeutic strategies will also be discussed.**

Keywords: Phenotypic plasticity; Epithelial-Mesenchymal Transition; Cancer stem cells; Vasculogenic mimicry

Received 28 October 2018, Revised 5 January 2019, Accepted 7 January 2019

*Corresponding Author: Yongfeng Jia, yfjia0471@163.com

1. Introduction

Tumor refers to the neogrowth induced by a variety of factors, also called neoplasm. With an increasing incidence worldwide, tumor has been the major leading cause of mortality. As a result, it is one of the most serious threats to health in the global population. Tumor cells have been considered with characteristics of excessive growth, even after lose stimulating factors. A fundamental question in the field is which cells can initiate tumors, and why tumors cannot stop growing? Therefore, how they affect and their interactions become experts' central arguments. As we know, canceration of healthy cells might be induced by multiple factors, such as environment, gene, variation and so on. Recently, researchers found a new factor, phenotypic plasticity, might also be closely related to process of canceration.

Phenotypic plasticity means the tissues or cells change phenotype, the term is also currently applied to the ability of a given cell type to reciprocally dedifferentiate, redifferentiate, and/or transdifferentiate in response to specific stimulation. Scientists have found that changes of phenotype exist both in normal and abnormal conditions. In normal conditions, cells function in the maintenance of tissue homeostasis or the restoration of tissue integrity following wounding or remodeling[1,2].

Compared with normal conditions, the plasticity potential of malignant cells has been more extensively studied in tumors as a mechanism that allows cells to transdifferentiate into mesenchymal cells and vice versa in a process highly controlled by the microenvironment[3]. More research works revealed that the functional consequences of this remarkable phenotypic plasticity, though not fully understood, may play a role in modulation of cell survival in suspension, chemoresistance, and intraperitoneal anchoring of metastatic lesions. Further, experts found three major pathways playing roles in tumor-inducing effects of phenotypic plasticity, which will be introduced one by one below.

2. Epithelial-Mesenchymal Transition

Epithelial-mesenchymal transition (EMT), is a part of normal physiological processes, including embryogenesis and wound healing[4].Recent research indicates that EMT is a dynamic process whereby epithelial cells lose polarity and cell-cell contacts, undergo dramatic remodeling of the cytoskeleton, acquire a migratory phenotype and a mesenchymal-like gene expression program. Both invasion and metastasis may be critically dependent on the acquisition by the incipient cancer cell of EMT features[5].

Researchers tried to investigate how EMT was modified by carcinoma cell phenotypic plasticity, in which cells of epithelial origin lose their epithelial characteristics and polarity and acquire a mesenchymal phenotype associated with increased migratory behavior[6-9], and activation of an EMT-like program in cancer cells was found in vitro similarly results in increased cell migration and invasion as well as increased resistance to apoptosis[10]. At the molecular level, EMT is characterized by 1) loss of expression of membranous E-cadherin, claudins, and occludins, 2)

increased expression of mesenchymal markers including vimentin and smooth muscle actin, 3) acquisition of a spindle-like morphology, and 4) cytoskeleton reorganization[11,12].

Tumor-associated EMT is currently viewed as a continuum of phenotypic plasticity and gain of mesenchymal characteristics. Process of tumor-associated EMT encompasses gradual disruption of epithelial architecture, resulting in discontinuity of basement membranes, loss of cellular cohesion, and altered apico-basal polarity[13]. This behavior is modified by carcinoma cell phenotypic plasticity that is evidenced by reversible switching between epithelial and mesenchymal phenotypes. Turmor-associated EMT has been strongly correlated with metastasis and shortened life expectancy of many carcinomas[14].

Rudolf Virchow proposed the hypothesis in 1893, that inflammation linked with tumor, and it have been confirmed later that chronic inflammation involved in tumor initiation, proliferation, invasion, metastasis and every stage of senescence and apoptosis[15]. There is a close link between inflammatory and tumor cell malignant transformation, and inflammation is also involved in the initiation and maintenance of EMT, EMT process may feedback and promote the formation of tumor microenvironment, maintain the inflammatory state further while enhance the ability of invasion and metastasis of tumor cells. It is similar between EMT and process of tumor cell dissemination, in which cells lose contact with the primary tumor and invade into the normal host tissue and blood vessels, these research has led to the hypothesis that EMT is an important part of the metastatic cascade[16]. It has been proposed that EMT in the human tumor setting may be transient and reversible, and that this phenotypic plasticity may be a key determinant of metastatic potential[17].

In addition to endow the migration and invasion of tumor cells, EMT can also make the tumor cells acquire characteristics of stem cells, including the ability to self-renew and efficiently initiate tumors so as to promote the cancer stem cell (cancer stem cells, CSCs) production[18,19].

3. Cancer Stem Cells

Tumors contain a few cells in a quiescent state that can be characterized as slow-cycling, expressing markers of stem cells and possessing the ability to initiate new tumors. These quiescent cells, now generally termed ‘cancer stem cells’ (CSC), or ‘cancer initiating cells’, are capable of regenerating the entire tumor—as it occurs in metastatic spread20. CSCs have the capacity of self-renewal and the potential to regenerate into all types of differentiated cells giving rise to heterogeneous tumor cell populations in a tumor mass, which contributes to tumor aggressiveness[21,22]. The biological characteristics determine that it plays a central role in tumor metastasis and recurrence.

Tumor heterogeneity has become an important theme of cancer research, one model predicts that metastasis and phenotypic heterogeneity is driven by specific gene expression programmes that are imposed by the cellular microenvironment rather than by the accumulation of genetic events[23], suggesting that tumors consist of multiple clonally derived subpopulations[24-26]. At the same time, it proved that large subpopulations of tumor cells are either capable of expansion or are terminally differentiated, while only a small subset of primitive, pluripotent CSC is capable of self-renewal, asymmetrical mitoses, and multi-lineage-specific differentiation.

Recent theories insist that CSCs are rarely part of stem cells and the power source of tumor formation. CSCs have the same signal transduction pathways, such as Wnt, Notch, Sonic hedgehog (Shh) and Bmi-1. CSCs have heterogeneity, for example, the clonal growth conditions in a patient with primary and metastatic foci, different metastasis and the same piece of tumor in different parts can be different. It can be speculated that the heterogeneity in this differentiation capacity may be one reason of tumor cell heterogeneity.

Research shows that the EMT process can induce some differentiated tumor cells form the characteristics of tumor stem cells[27, 28]. This study linked CSCs and EMT closely and suggested that CSCs could be the basis of tumor invasion and metastasis. CSCs induced EMT and enhance the ability of invasion29. The interaction between EMT and CSCs cooperate in breast cancer, as induction of EMT enhances self-renewal and expression of cancer stem cells, which are believed to facilitate tumor resistance supporting the idea that a stem-cell phenotype may be important in the epithelial plasticity of the cell line[30].

4. Vasculogenic Mimicry

Research has shown that the plastic notion of some highly aggressive tumor such as melanoma is characterized by the concurrent expression of genes from a variety of different cell types, including stem cells, concomitantly with reduced melanoma associate gene expression[31]. In particular, highly aggressive melanoma cells, in contrast to poorly aggressive ones, display substantial plasticity, exemplified by the formation of tube-like structures termed Vasculogenic mimicry (VM) which was demonstrated as an example of the remarkable plasticity displayed by aggressive melanoma cells[32,33]. It suggests that these tumor cells have acquired an embryonic-like phenotype[34].

Turmor requires an adequate blood supply to sustain rapid growth[35]. It was believed that only endothelial cells could form blood vessels. However, when endothelium-dependent vessel growth is insufficient to support the rapid proliferation of tumor tissues, highly

aggressive and metastatic melanoma cells can form vascular channel-like structures that are independent of angiogenesis through process of VM[32]. VM was introduced by Maniotis in 1999 to describe the unique ability of highly aggressive tumor cells to form capillary-like and extracellular matrix-rich tubular networks without the participation of endothelial cells[32,36], and gradually found in ovarian[37], breast[38], liver and stomach cancer[39,40]. Further studies demonstrated that VM only occurs in extremely malignant tumors and hypoxia can promote its formation in these tumors[39,41]. VM has also been found in malignant glioblastomas, and the induced hypoxic condition has been found to affect the VM formation of gliomas[42,43].

VM means cells can mimic vascular structure to form system to convey blood through its deformation and cell extracellular matrix interactions. It provides a perfusion pathway for rapidly growing tumors, transporting fluid from leaky vessels, and/or connecting with endothelial-lined vasculature as well as an escape route for metastasis. VM is the dominant method that provides the blood supply in the early stage of cancer and is also an important route of metastasis[44]. The special structure of VM promotes tumor cell metastasis. Without barrier, tumor cells, composed of VM, contact with blood directly, and will flow with blood to distant tissues. VM increases the perfusion of rapidly growing tumors by transporting fluid from leaky vessels, and VM tubes may even connect with the endothelial-lined vasculature[45,46]. Experts indicated that VM refers to the process by which highly aggressive tumor cells mimic endothelial cells to form vessel-like structures that aid in supplying enough nutrients to rapidly growing tumors[47].

VM characteristics can be summarized as follows: (1) positive PAS and negative CD31 straining; (2) the channel is lined by tumour cells rather than endothelial cells; (3) the expression of a multipotent, stem cell-like phenotype; (4) ECM remodeling and (5) VM has connection with the tumour microcirculation system, providing blood for tumor growth[48,49].Generally speaking, VM's mechanisms underlying its formation remain unclear, but a variety of proteins and micro-environmental factors are known to contribute to it[49,50]. For example, the changing tumor microenvironment has a certain promoting effect on VM. Hypoxia and tumor extracellular matrix remodeling are also actively involved in VM formation[51,52]. In addition to HIF-1α and VEGF, which contribute to the mechanisms of VM formation, another known factor that promotes the VM formation of highly malignant glioma cells is the hypoxic condition[53,54].

5. EMT, CSCs and VM

Recently mounting studies implicated CSCs in VM formation. Experts proved that hypoxia induces VM, and CSCs may play an important role in VM[55-57]. For example, administration of anti-angiogenic agents induces intratumoral hypoxia, and hypoxia increases the number of CSCs in cell lines derived from glioblastomas and breast cancers[34]. Then, it was hypothesized that intratumoral hypoxia induced by anti-angiogenic agents accelerates VM channel formation by increasing the population of CSCs, which in turn, causes tumor regrowth, metastases, and treatment failure using anti-angiogenic agents[58].

With increasing studies on CSC's origin, mounting data suggest that differentiated tumor cells may reacquire stemness[48], particularly via EMT induction[59]. Further research suggested that EMT might be involved in CSCs formation[60,61]. The endowment of stem cell traits by EMT provided another source for the origin of CSCs. Both epithelial and mesenchymal markers have been observed in tumor cells engaged in VM formation[62,63]. Therefore, in view of the crucial role of EMT in the acquisition of stemness, it is plausible that CSCs are implicated in VM formation by induction of EMT.

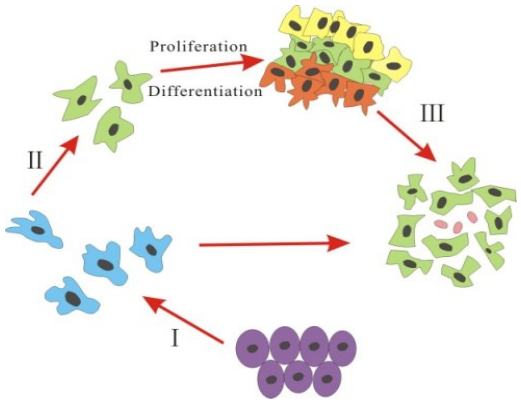

Figure 1. The relationship between EMT and CSCs and VM. Ⅰ) Tumor cells of epithelial origin lose their epithelial characteristics and polarity and acquire a mesenchymal phenotype associated with increased migratory behavior. Ⅱ) Part of tumor cells reacquire stemness particularly via EMT induction. Ⅲ) Tumor cells continue to proliferate and differentiate and led to hypoxia. Then highly aggressive and metastatic cells form vascular channel-like structures to requires an adequate blood supply to sustain rapid growth.

Recently, EMT has been reported to contribute to the formation of VM, and the upregulation of EMT-associated transcription factors has been demonstrated in VM-forming tumor cells[64,65],It is interesting to speculate that highly aggressive epithelial tumor cells may likewise overexpress the mesenchymal phenotype through EMT during VM formation. Changing of EMT is accompanied by the presence of VM. Wang illustrated that EMT regulated by EphA2 contributed to VM formation in head and neck squamous cell carcinoma[66,67]. These findings

may support the idea that VM formation may be part of EMT. Above all, we may come to this conclusion that these findings widely suggested that CSC may be involved in VM formation by EMT induction (Figure 1).

6. Discussion

EMT, CSCs and VM take part in the modulating of phenotypic plasticity in tumor cells, and their coexistences especially in aggressive tumors indicates there might be interactions between them. Phenotypic plasticity and the underlying EMT, CSCs and VM process contribute to resistance to chemotherapy and radiotherapy, and lower survival rate in tumor patient. A combination of targeting EMT, CSCs, VM and phenotypic transition will not only provide a solid rationale to evaluate the antitumorigenic potential of therapeutic agents, but also be beneficial for better understanding of tumor progression and phenotypic plasticity, and improving survival rate of tumor patients.

Conflict of interest

The authors indicate no potential conflict of interest.

Acknowledgements

This project was supported by Grants from the National Natural Science Foundation of China (No. 81260393), Program for Young Talents of Science and Technology in Universities of Inner Mongolia Autonomous Region (No. NJYT-14-A11),the “Chunhui Plan” of Ministry of Education (No.Z2012010), the Science and Technology Research Projects of Higher Education Institutions of Inner Mongolia Autonomous Region (No.NJZY12142) and the applied technology research and development funds of the Inner Mongolia autonomous region(No. kjt13sf03), the Natural Science Foundation of Inner Mongolia Autonomous Region(No. 2015MS(LH)0807).

References

[1] Cardiff RD, Couto S, Bolon B. Three interrelated themes in current breast cancer research: gene addiction, phenotypic plasticity, and cancer stem cells[J]. Breast cancer research: BCR, 2011, 25, 13(5):216.

[2] Hoek KS, Goding CR. Cancer stem cells versus phenotype-switching in melanoma[J]. Pigment cell & melanoma research, 2010, 23(6):746-59.

[3] Hudson LG, Zeineldin R, Stack MS. Phenotypic plasticity of neoplastic ovarian epithelium: unique cadherin profiles in tumor progression[J]. Clinical & experimental metastasis, 2008, 25(6):643-55.

[4] Savagner P. Leaving the neighborhood: molecular mechanisms involved during epithelial-mesenchymal transition[J]. BioEssays: news and reviews in molecular, cellular and developmental biology, 2001, 23(10):912-23.

[5] Zuo J, Wen J, Lei M, et al. Hypoxia promotes the invasion and metastasis of laryngeal cancer cells via EMT[J]. Medical oncology, 2016, 33(2):15.

[6] Christ B, Ordahl CP. Early stages of chick somite development[J]. Anatomy and embryology, 1995, 191(5):381-96.

[7] La Belle AA, Schiemann WP. The propensity for epithelial-mesenchymal transitions is dictated by chromatin states in the cancer cell of origin[J]. Stem cell investigation, 2017, 4:44.

[8] Savagner P. Epithelial-mesenchymal transitions: from cell plasticity to concept elasticity[J]. Current topics in developmental biology, 2015, 112:273-300.

[9] Marchesi V. Breast cancer: Epithelial-mesenchymal transitions in human breast cancer samples[J]. Nature reviews Clinical oncology, 2013, 10(4):184.

[10] Thompson EW, Newgreen DF, Tarin D. Carcinoma invasion and metastasis: a role for epithelial-mesenchymal transition? [J]. Cancer research, 2005, 65(14):5991-5.

[11] Thiery JP. Epithelial-mesenchymal transitions in development and pathologies[J]. Current opinion in cell biology, 2003, 15(6):740-746.

[12] Kalcheim C. Epithelial-Mesenchymal Transitions during Neural Crest and Somite Development. Journal of clinical medicine, 2015, 25:5(1).

[13] Gao D, Vahdat LT, Wong S, et al. Microenvironmental regulation of epithelial-mesenchymal transitions in cancer[J]. Cancer research, 2012, 72(19):4883-4889.

[14] Zhou JN, Zeng Q, Wang HY, et al. MicroRNA-125b attenuates epithelial-mesenchymal transitions and targets stem-like liver cancer cells through small mothers against decapentaplegic 2 and 4[J]. Hepatology, 2015, 62(3):801-815.

[15] Kovacic JC, Mercader N, Torres M, et al. Epithelial-to-mesenchymal and endothelial-to-mesenchymal transition: from cardiovascular development to disease[J]. Circulation, 2012, 125(14):1795-808.

[16] Yang J, Weinberg RA. Epithelial-mesenchymal transition: at the crossroads of development and tumor metastasis[J]. Developmental cell, 2008, 14(6):818-829.

[17] Hollier BG, Evans K, Mani SA. The epithelial-to-mesenchymal transition and cancer stem cells: a coalition against cancer therapies[J]. Journal of mammary gland

biology and neoplasia, 2009, 14(1):29-43.
[18] Shekhani MT, Jayanthy AS, Maddodi N, et al. Cancer stem cells and tumor transdifferentiation: implications for novel therapeutic strategies[J]. American journal of stem cells, 2013, 2(1):52-61.
[19] Tirino V, Desiderio V, Paino F, et al. Cancer stem cells in solid tumors: an overview and new approaches for their isolation and characterization[J]. FASEB journal: official publication of the Federation of American Societies for Experimental Biology, 2013, 27(1):13-24.
[20] Shackleton M. Normal stem cells and cancer stem cells: similar and different[J]. Seminars in cancer biology, 2010, 20(2):85-92.
[21] Creighton CJ, Chang JC, Rosen JM. Epithelial-mesenchymal transition (EMT) in tumor-initiating cells and its clinical implications in breast cancer[J]. Journal of mammary gland biology and neoplasia, 2010, 15(2):253-260.
[22] Hennessy BT, Gonzalez-Angulo AM, Stemke-Hale K, et al. Characterization of a naturally occurring breast cancer subset enriched in epithelial-to-mesenchymal transition and stem cell characteristics[J]. Cancer research, 2009, 69(10):4116-4124.
[23] Croker AK, Allan AL. Cancer stem cells: implications for the progression and treatment of metastatic disease[J]. Journal of cellular and molecular medicine, 2008, 12(2):374-390.
[24] Patel SA, Ndabahaliye A, Lim PK, et al. Challenges in the development of future treatments for breast cancer stem cells[J]. Breast Cancer (Dove Med Press), 2010, 2:1-11.
[25] Raimondi C, Gianni W, Cortesi E, et al. Cancer stem cells and epithelial-mesenchymal transition: revisiting minimal residual disease[J]. Current cancer drug targets, 2010,10(5):496-508.
[26] Ma SR, Wang WM, Huang CF, et al. Anterior gradient protein 2 expression in high grade head and neck squamous cell carcinoma correlated with cancer stem cell and epithelial mesenchymal transition[J]. Oncotarget, 2015, 6(11):8807-8821.
[27] Le NH, Franken P, Fodde R. Tumour-stroma interactions in colorectal cancer: converging on beta-catenin activation and cancer stemness[J]. British journal of cancer, 2008, 98(12):1886-93.
[28] Zhifang M, Liang W, Wei Z, et al. The androgen receptor plays a suppressive role in epithelial- mesenchymal transition of human prostate cancer stem progenitor cells[J]. BMC biochemistry, 2015, 16:13.
[29] Qu Y, Zhang L, Rong Z, et al. Number of glioma polyploid giant cancer cells (PGCCs) associated with vasculogenic mimicry formation and tumor grade in human glioma[J]. Journal of experimental & clinical cancer research: CR2013, 32:75.
[30] Larson AR, Lee CW, Lezcano C, et al. Melanoma spheroid formation involves laminin-associated vasculogenic mimicry[J]. The American journal of pathology, 2014, 184(1):71-78.
[31] Hendrix MJ, Seftor EA, Hess AR, et al Molecular plasticity of human melanoma cells[J]. Oncogene, 2003, 22(20):3070-3075.
[32] Maniotis AJ, Folberg R, Hess A, et al. Vascular channel formation by human melanoma cells in vivo and in vitro: vasculogenic mimicry[J]. The American journal of pathology, 1999, 155(3):739-752.
[33] Wang H, Sun W, Zhang WZ, et al. Inhibition of tumor vasculogenic mimicry and prolongation of host survival in highly aggressive gallbladder cancers by norcantharidin via blocking the ephrin type a receptor 2/focal adhesion kinase/paxillin signaling pathway[J]. PloS one, 2014, 9(5):e96982.
[34] Liu T, Sun B, Zhao X, et al. OCT4 expression and vasculogenic mimicry formation positively correlate with poor prognosis in human breast cancer[J]. International journal of molecular sciences, 2014, 15(11):19634-1949.
[35] Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis[J]. Cell, 1996, 86(3):353-364.
[36] Zhao X, Sun B, Li Y, et al. Dual effects of collagenase-3 on melanoma: metastasis promotion and disruption of vasculogenic mimicry[J]. Oncotarget, 2015, 6(11):8890-8899.
[37] Sood AK, Fletcher MS, Zahn CM, et al. The clinical significance of tumor cell-lined vasculature in ovarian carcinoma: implications for anti-vasculogenic therapy[J]. Cancer biology & therapy, 2002, 1(6):661-664.
[38] Shirakawa K, Kobayashi H, Sobajima J, et al. Inflammatory breast cancer: vasculogenic mimicry and its hemodynamics of an inflammatory breast cancer xenograft model[J]. Breast cancer research: BCR, 2003, 5(3):136-139.
[39] Guzman G, Cotler SJ, Lin AY, et al. A pilot study of vasculogenic mimicry immunohistochemical expression in hepatocellular carcinoma[J]. Archives of pathology & laboratory medicine, 2007, 131(12):1776-1781.
[40] Fujimoto A, Onodera H, Mori A, et al. Tumour plasticity and extravascular circulation in ECV304 human bladder carcinoma cells[J].

Anticancer research, 2006, 26(1A):59-69.
[41] Wohlfart P, Malinski T, Ruetten H, et al. Release of nitric oxide from endothelial cells stimulated by YC-1, an activator of soluble guanylyl cyclase[J]. British journal of pharmacology, 1999, 128(6):1316-1322.
[42] El Hallani S, Boisselier B, Peglion F, et al. A new alternative mechanism in glioblastoma vascularization: tubular vasculogenic mimicry[J]. Brain : a journal of neurology, 2010, 133(Pt 4):973-982.
[43] Li J, Ke Y, Huang M, et al. Inhibitory effects of B-cell lymphoma 2 on the vasculogenic mimicry of hypoxic human glioma cells[J]. Experimental and therapeutic medicine, 2015, 9(3):977-981.
[44] Zhang S, Guo H, Zhang D, et al. Microcirculation patterns in different stages of melanoma growth[J]. Oncology reports, 2006, 15(1):15-20.
[45] Wang L, Lin L, Chen X, et al. Metastasis-associated in colon cancer-1 promotes vasculogenic mimicry in gastric cancer by upregulating TWIST1/2[J]. Oncotarget, 2015, 6(13):11492-11506.
[46] Cui YF, Liu AH, An DZ, et al. Claudin-4 is required for vasculogenic mimicry formation in human breast cancer cells[J]. Oncotarget, 2015, 6(13):11087-11097.
[47] Shirakawa K, Wakasugi H, Heike Y, et al. Vasculogenic mimicry and pseudo-comedo formation in breast cancer[J]. International Journal of Cancer, 2002, 99(6):821-8.
[48] Qiao L, Liang N, Zhang J, et al. Advanced research on vasculogenic mimicry in cancer[J]. Journal of cellular and molecular medicine, 2015, 19(2):315-326.
[49] Paulis YW, Soetekouw PM, Verheul HM, et al. Signalling pathways in vasculogenic mimicry[J]. Biochimica et biophysica acta, 2010, 1806(1):18-28.
[50] Kirschmann DA, Seftor EA, Hardy KM, et al. Molecular pathways: vasculogenic mimicry in tumor cells: diagnostic and therapeutic implications[J]. Clinical cancer research: an official journal of the American Association for Cancer Research, 2012, 18(10):2726-32.
[51] Gov E, Kori M, Arga KY. Multiomics Analysis of Tumor Microenvironment Reveals Gata2 and miRNA-124-3p as Potential Novel Biomarkers in Ovarian Cancer[J]. Omics: a journal of integrative biology, 2017.
[52] Florczyk SJ, Wang K, Jana S, et al. Porous chitosan-hyaluronic acid scaffolds as a mimic of glioblastoma microenvironment ECM[J]. Biomaterials, 2013, 34(38):10143-50.
[53] Tafani M, Di Vito M, Frati A, et al. Pro-inflammatory gene expression in solid glioblastoma microenvironment and in hypoxic stem cells from human glioblastoma[J]. Journal of neuroinflammation, 2011, 8:32.
[54] Heddleston JM, Wu Q, Rivera M, et al. Hypoxia-induced mixed-lineage leukemia 1 regulates glioma stem cell tumorigenic potential[J]. Cell death and differentiation, 2012, 19(3):428-39.
[55] Guelfi S, Duffau H, Bauchet L, et al. Vascular transdifferentiation in the CNS: a focus on neural and glioblastoma stem-like cells[J]. Stem cells international, 2016, 2016:2759403.
[56] Sun B, Zhang D, Zhang S, et al. Hypoxia influences vasculogenic mimicry channel formation and tumor invasion-related protein expression in melanoma[J]. Cancer letters, 2007, 249(2):188-197.
[57] Liu TJ, Sun BC, Zhao XL, et al. CD133+ cells with cancer stem cell characteristics associates with vasculogenic mimicry in triple-negative breast cancer[J]. Oncogene, 2013, 32(5):544-553.
[58] Lee G, Auffinger B, Guo D, et al. Dedifferentiation of Glioma Cells to Glioma Stem-like Cells By Therapeutic Stress-induced HIF Signaling in the Recurrent GBM Model[J]. Molecular cancer therapeutics, 2016, 15(12):3064-3076.
[59] Notta F, Mullighan CG, Wang JC, et al. Evolution of human BCR-ABL1 lymphoblastic leukaemia-initiating cells[J]. Nature, 2011, 469(7330):362-367.
[60] Xia H, Cheung WK, Sze J, et al. miR-200a regulates epithelial-mesenchymal to stem-like transition via ZEB2 and beta-catenin signaling[J]. The Journal of biological chemistry, 2010, 285(47):36995-7004.
[61] Fang X, Cai Y, Liu J, et al. Twist2 contributes to breast cancer progression by promoting an epithelial-mesenchymal transition and cancer stem-like cell self-renewal[J]. Oncogene, 2011, 30(47):4707-4720.
[62] Su M, Feng YJ, Yao LQ, et al. Plasticity of ovarian cancer cell SKOV3ip and vasculogenic mimicry in vivo[J]. International journal of gynecological cancer: official journal of the International Gynecological Cancer Society, 2008, 18(3):476-486.
[63] Hendrix MJ, Seftor EA, Hess AR, et al. Vasculogenic mimicry and tumour-cell plasticity: lessons from melanoma. Nature reviews Cancer, 2003, 3(6):411-421.
[64] Pisacane AM, Picciotto F, Risio M. CD31 and CD34 expression as immunohistochemical markers of endothelial transdifferentiation in human cutaneous melanoma[J]. Cellular oncology: the official journal of the International Society for Cellular Oncology,

2007, 29(1):59-66.
[65] Liu Z, Sun B, Qi L, et al. Zinc finger E-box binding homeobox 1 promotes vasculogenic mimicry in colorectal cancer through induction of epithelial-to-mesenchymal transition[J]. Cancer science, 2012, 103(4):813-820.
[66] Wang W, Lin P, Sun B, et al. Epithelial-mesenchymal transition regulated by EphA2 contributes to vasculogenic mimicry formation of head and neck squamous cell carcinoma[J]. BioMed research international, 2014, 2014:803914.
[67] Zhao XL, Sun T, Che N, et al. Promotion of hepatocellular carcinoma metastasis through matrix metalloproteinase activation by epithelial-mesenchymal transition regulator Twist1[J]. Journal of cellular and molecular medicine, 2011, 15(3):691-700.

