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EMT-like process in glioblastomas and reactive astrocytes

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ABSTRACT

The concept of the epithelial-to-mesenchymal transition (EMT) in epithelial cells has accelerated our understanding about cancer spreading. Fortunately, much of this information has been able to be extrapolated to non-epithelial cancers, such as glioblastoma (GBM). Interestingly, reactive astrocytes, which are present in the tumor edge in association with glioma cells, might also undergo EMT-like under stimuli of GBM cells. As result, the positive feedback of reactive astrocytes and glioma cells, could act to promote cancer progression making use of the dynamism of the mesenchymal phenotype. Nonetheless, the interpretation of data regarding EMT-like in GBM and astrocytes requires prudence, mainly because the program of EMT in epithelial tumors may not necessarily be the same as those in gliomas and astrocytes.

1. Introduction

Epithelial-to-mesenchymal transition (EMT) is a cell-biological process that plays key roles in embryogenesis and wound healing. The significant parallels between cell plasticity during embryonic development and carcinoma progression have helped us understand the importance of the EMT in human disease. Our expanding knowledge of EMT has led to a clarification of the EMT program as a set of multiple and dynamic transitional states between the epithelial and mesenchymal phenotypes, as opposed to a process involving a single binary state. EMT and its intermediate states have recently been identified as crucial drivers of organ fibrosis and tumor progression.

Here we discuss the current state-of-the-art and latest findings regarding the concept of cellular plasticity and heterogeneity of EMT focusing in astrocytes cells. We raise some of the questions pending and identify challenges faced in this fast-moving field.

2. EMT: Epithelial to mesenchymal transition

EMT was first described as a mechanism driving critical morphogenetic steps (for example, gastrulation) in the development of most metazoans (Jordan et al., 2011; Lim and Thiery, 2012) and, more recently, in wound-healing and carcinoma progression (Thiery et al., 2009).

According to the traditional definition of EMT, this process is a highly regulated transdifferentiation cellular program, by which epithelial cells can move toward the mesenchymal state with a progressive acquisition of motile and invasive behavior, characterized by changes in gene expression that culminates in loss of epithelial characteristics and the acquisition of mesenchymal features (Lee et al., 2006). EMT induces altered cell polarity, weak cell-cell adhesion ability and enhanced migratory capacity. Besides, cells in transition display altered morphology, chemoresistance and stem cell properties. The reverse of this process, mesenchymal-to-epithelial transition (or MET), is associated with a loss of this migratory freedom, with cells re-acquiring apico-basal polarization and expressing genes responsible for the epithelial cell phenotype. An important point is that the most of the time, cells are able to transit between different levels of epithelial and mesenchymal phenotypes in a very plastic and dynamic manner (Lee et al., 2006; Kalluri and Weinberg, 2009; Nieto et al., 2016).

Many pleiotropic signaling factors (e.g., growth factors, cytokines, chemokines, and others) may induce EMT by inducting the expression of specific transcription factors (e.g., ZEB1, ZEB2, SNAI1, SNAI2 (SLUG), TWIST, and others) and miRNAs. An increase in levels of the EMT-inducing transcription factors can result in loss of membranous localization of the epithelial marker E-cadherin, increased levels of one or more mesenchymal markers, such as vimentin, N-cadherin, alfa-smooth muscle actin, or fibronectin, culminating with a loss of polar-

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ized function of epithelial cells. The cadherin switch, characterized by loss of functional E-cadherin with the concomitant up-regulation of N-cadherin is a hallmark of the EMT process (Cano et al., 2000; Thiery, 2002).

3. EMT spectrum

Although EMT suggests a shift between two alternative states, totally mesenchymal or purely epithelial, recent works evidenced that indeed cells fluctuate through a spectrum of intermediary states. These intermediary stages of plasticity have been frequently observed in different experimental models and referred to as partial EMT, hybrid intermediate EMT, metastable, incomplete ETM or EMT-like (Grigore et al., 2016). The EMT-like is characterized by cells that retain some epithelial features, while acquire mesenchymal characteristics, or even, cells with reduced epithelial properties, but not necessarily gaining mesenchymal traits. This intermediate state may permit the cells to either reverse to an epithelial state or progress to a mesenchymal phenotype, allowing a greater control over cell processes such as migration, invasion and stemness maintenance (Huang et al., 2012).

Faced to the expanding knowledge about partial EMT, it is important the researchers keep in mind that probably in most experimental models, pronounced change in the expression of epithelial (E-cadherin, cytokeratin, claudin, occludin) and mesenchymal markers (N-cadherin and vimentin) will not be observed (Thiery and Sleeman, 2006; Thiery et al., 2009; Grigore et al., 2016). Moreover, in many cases, the traditional E-to-N-cadherin switch may do not even occur (Auersperg et al., 1999; Asano et al., 2004; Camand et al., 2012) during the dynamic process of partial EMT. This is explained by the dynamism of cell phenotype during tumor progression, which consequently makes it almost impossible to isolate population of cells with a homogeneous phenotype in experimental models. This is intensified by the greatly heterogeneity of cells that compound the tumor mass (Grigore et al., 2016).

Huang and colleagues analyzed 43 ovarian cancer cell lines and observed that approximately 20% of cells presented an intermediate phenotype, co-expressing epithelial and mesenchymal markers (e-cadherin, cytokeratin and vimentin). Interestingly, 45% of these intermediate cells co-expressed both E− and N-cadherin at the cell surface (Huang et al., 2013). Lung adenocarcinoma cell lines also presented E-cadherin and vimentin co-expression (Jolly et al., 2016). Using human breast cancer cell lines, it was observed that hypoxia, a well known inductor of EMT, induced Snail expression, however, not accompanied by an increased in cell motility (Lundgren et al., 2009). The hybrid phenotype is also associated with stemness and poor prognosis in patients with breast tumor (Grosse-Wilde, Fouquier d'Herouel et al., 2015). In addition, the mesenchymal status in different tumors is not necessarily correlated to resistance to chemotherapy (Tan et al., 2014), evidencing the complex role of EMT in tumor progression.

The difficulty to elucidate the EMT score can also explains the differences in EMT in different tumors. It is very difficult to compare tumors of different origins and extremely daring to define the exact impact of mesenchymal-epithelial phenotypes in tumor progression of each different tumor type. More likely, processes such as chemoresistance and metastasis are not exclusively associated to mesenchymal traits and possibly theirs association may be susceptible to the environment influence, such as drug treatment, cytotoxic stress, and others.

It is evident that the fully epithelial and fully mesenchymal phenotypes are uncommon to be observed in tumor mass. Thus, the comprehension of the EMT program could contribute with the understanding of these different phenotypic gradients, enabling the treatment of tumors with different combinations of drugs, for each phenotypic stage of cells.

4. The developmental origin of glial cells

Tan and colleagues established a method to quantify the EMT spectrum in clinical samples and cell lines through transcriptomics. They used this EMT score to situate different cancer types on a scale ranging from mesenchymal-like (Mes) to epithelial-like (Epi) characteristics. Interestingly, they observed that the EMT score was closely related to the tumor type. For example, whereas colorectal, bladder and gastric cancers were predominantly epi, renal carcinoma, malignant melanoma, sarcoma and glioblastoma were primarily Mes (Tan et al., 2014). In a similar way, in order to position the gliomas in an epithelial/mesenchymal (Epi/Mes) transcriptional scale, we developed a mesenchymal and epithelial metasignature based on TGFβ-induced EMT in lung adenocarcinoma cells. Interestingly, similarly to their study, we showed that most gliomas presented a more mesenchymal phenotype (Iser et al., 2017).

The explanation for these results could be the origin of cells. Most gliomas are probably derived from transformed neural progenitor cells (Nakaya and Sheng, 2013), which originate from the neural crest. During the development of the vertebrate nervous system, the epithelial neural plate in the midline of the embryo rolls up to form the neural tube, precursor of the brain and spinal cord. Those epithelial cells located near the dorsal midline of the neural tube, undergo primary EMT to become migratory neural crest cells, which subsequently move away from the neural tube, crossing throughout the embryo. Following their migration, neural crest cells differentiate into many diverse derivatives, including ganglia of the peripheral nervous system, bone and cartilage of the jaws, pigment cells, and glial cells (Acloque et al., 2009). Thus, these neural crest cell derivatives maintain an intrinsic Mes phenotype, which could explain the Mes trait of gliomas finding in our study.

Although these phenotypic traits may be related to origin or the lineage of the cancer, extrinsic factors, such as the tumor microenvironment, may also interfere in the primary features of tumors cells, modulating the EMT score.

5. EMT-Like in glial cells

In the recent years, many authors have demonstrated that cells that compound the tumor microenvironment, such as mesenchymal stem cells and fibroblasts, can affect EMT process in tumor cells of different tumor models. In the same line, we have shown that conditioned medium of rat adipose-derived stem cells (ADSCs) induces epithelial-to-mesenchymal-like transition (EMT-like) in glioblastoma (GBM) cells marked by reduced cell adhesion ability, enhanced migration capacity and presence of changes in cell morphology, including nuclei irregularities (Iser et al., 2016).

Interestingly, although the activation of EMT-like process has been described to be important for glioma progression, both GBM and astrocytes are not typical epithelial cells and therefore the classical EMT that starts with an epithelial cell does not apply. This is reinforced by the almost complete lack of detected metastasis from GBM, in contrast to epithelial tumors. In addition, this question is complicated by the inconsistency in the literature, with some reports showing that GBMs do not express E-cadherin, but others showing the occurrence of E− and N-cadherin switch.

Faced with the scarcity of scientific information about EMT in gliomas, we elaborated a systematic review and an *in silico* investigation to better understand the process of EMT-like in GBM (Iser et al., 2017). The analysis using transcriptomic databases to investigate the expression of E− and N-cadherin in human GBM samples from TCGA, showed that the majority of GBM samples analyzed, have a higher expression of N-cadherin in comparison to E-cadherin, very similarly to the ratio of N-cadherin expressed by lung adenocarcinoma cells, after TGFβ-induced EMT. These results support the notion that the EMT in GBM is not identical to EMT in epithelial tumors and although cadherin switching is a central process of EMT in epithelial cells, it seems not to be essential for all aspects of EMT-like in non-epithelial cells. In addition, we discussed that while the epithelial to mesenchymal switch is well described in normal epithelial cells (cells of origin of carcinomas), no information was found about the EMT-like process in astrocytes, cells with which GBM and other types of astrocytomas share morphological characteristics (Iser et al., 2017).

In our review, we explored and dissected a broad set of scientific information about epithelial and mesenchymal characteristics in astrocytes and interestingly, we found that astrogliosis, a process that promotes changes in astrocytes cells in response to several forms of central nervous system injury and disease, share some similarities with EMT. For example, reactive astrocytes up-regulate N-cadherin after brain injury (Kanemaru et al., 2013). Thus, we raised the hypothesis that astrocytes, in some way and in special circumstances, could undergo the EMT-like process. Faced with this hypothesis, we performed *in silico* analysis in order to position normal murine glial cells in an epithelial-mesenchymal gradient. Thereby, we created a metasignature based on gene expression of lung carcinoma cells induced and non-induced to EMT by TGF-β. Surprisingly, we observed that murine glial cells present a more mesenchymal state, when compared to GBM or lung carcinoma, indicating that the EMT in astrocytes, if present, is not an obvious process (Iser et al., 2017). These results let us to question whether astrocytes could really adopt an even more mesenchymal phenotype.

Interestingly, Okolie and colleagues showed that some circumstances, such as trauma induced by tumor surgical resection could modify the reactive astrocytes present in the peritumoral microenvironment, inducing a stem cell–like phenotype in these cells. In addition, these astrocytes are able to promote tumor proliferation and migration, enhancing tumor aggressiveness (Okolie et al., 2016).

Using rat astrocytes culture treated with conditioned medium from a glioma cell line, Lu and colleagues showed that the astrocytes activated by glioma cells presented mesenchymal-like characteristics, such as enhanced migration and invasion activity, decreased expression of E-cadherin and concomitant increased expression of vimentin and matrix metalloproteinases, in relation to untreated cells. In this way, it was observed that besides inducing the activation of astrocytes, glioma cells might induce a EMT-like process via upregulation of Wnt/β-catenin signaling (Lu et al., 2016).

Alterations in gene expression after co-culture of astrocytes and U87 glioma cell line were also demonstrated, however not presenting direct correlation with EMT process. The authors observed that besides triggering astrocyte activation by GFAP overexpression, U87 cells promote up-regulation of the invasion-related proteins MMP-2 and SPARC, suggesting that glioma cells could stimulate specific phenotype modifications in astrocytes (Gagliano et al., 2009). On the same line, Kanemaru and colleagues showed that reactive astrocytes presented altered expression of many genes and exhibit distinct morphological and functional features, when compared with nonreactive astrocytes. Among the genes with altered expression during reactive astrogliosis after brain injury, N-cadherin was up-regulated (Kanemaru et al., 2013).

These results reinforce the idea that reactive gliosis is a highly heterogeneous state, in which astrocyte activities are altered to respond to the specific injury. It is still very difficult to determine the exact time that cells undergo the EMT-like process. The induction and response to EMT stimuli are very transient, which makes it very difficult to know how and when these processes actually take place *in vivo*.

Although the EMT-like process is not well elucidated in astrocytes, there is evidence that it is one of the mechanisms by which reactive astrocytes contribute to tumor progression in gliomas, thereby, establishing a synergistic relation with GBM cells. For example, reactive astrocytes produce connective tissue growth factor (CTGF) that induces the expression of ZEB1 by tumor cells, stimulating EMT-like and tumor cell infiltration (De Vleeschouwer and Bergers, 2017). In addition, astrocytes also release a wide variety of other molecules involved to EMT, such as matrix metalloproteinases (MMPs), tumor growth factor β (TGFβ), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF) and stromal cell-derived factor 1 (SDF-1) (Jha et al., 2018). The release of these factors promotes the crosstalk between two cell populations leading to proliferation, migration and invasion of tumor cells (Guan et al., 2018).

A recent report showed that the communication between reactive astrocytes and glioma cells could also occur through ion channels and ion transporters. These channels allow changes in ion concentrations, such as H^+, K^+ and Ca^{2+}, stimulating cell volume variations, loss of epithelial polarization of glioma cells, increasing migratory capacity and invasiveness of tumor cells, in line with the EMT-like program (Guan et al., 2018). Other form of communication between astrocytes and GBM cells involves gap junctions. For example, the expression of gap junctional protein connexin43 (Cx43) is upregulated in glioma-associated astrocytes, promoting chemotherapy resistance, glioma cell proliferation and migration. These data show that, once activated by neighboring glioma cells, the astrocytes interact in a complex way with the tumor microenvironment, promoting cell proliferation, invasion, and, ultimately, providing a favorable environment to the development of the EMT-like process (Guan et al., 2018).

The results about the EMT-like process in GBM and astrocyte seem very promising, however, there is some need for caution when interpreting the results, once apparently the changes that GBM and astrocytes undergo are similar, but are not identical to the classic EMT observed in epithelial cells.

In view of these results, we proposed a model in which normal astrocytes undergo different phenotypic changes when associated to GBM, which includes changes similar to EMT, especially when undergoing astrogliosis (Fig. 1). In a similar way, under some conditions, GBM can acquire more mesenchymal profile, which can be associated to an invasive phenotype (Fig. 1). In this context, glioma cells and astrocytes can potentially function in a positive-feedback way, with glioma cells, inducing mesenchymal-like transition in astrocytes, which in turn would promote changes in the surrounding microenvironment, stimulating tumor invasion and spreading.

In summary, it is evident that the mechanisms that govern the changes in astrocytes and GBM are non-linear, and many regulatory networks may drive the EMT-like event in different cells and a crosstalk between astrocytes activated by the damage produced by the growing tumor and the tumor cells itself can reinforce the more invasive and aggressive mesenchymal phenotype in the latter cells.

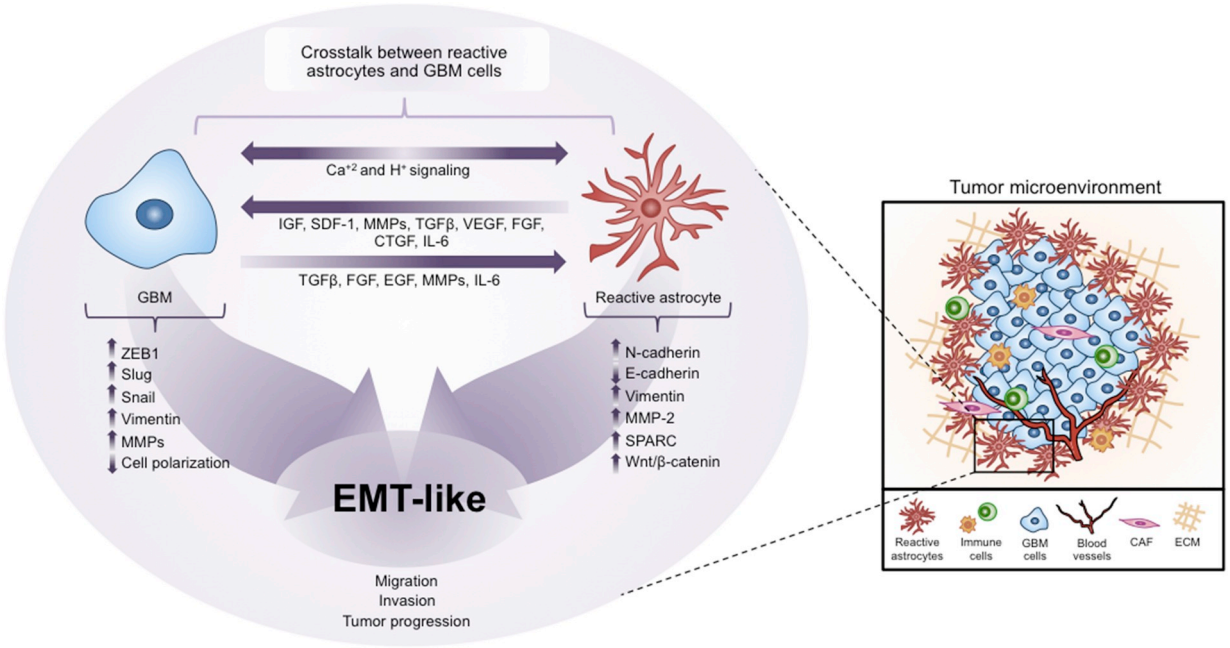

Fig. 1. Astrocytes and glioma crosstalk promotes phenotypic mesenchymal changes and tumor progression. GBM cells are surrounded by a microenvironment that consists of numerous cells such as endothelial cells of blood vessels, different types of immune cells, CAFs and an abundant quantity of ECM, composed mainly by proteins such as laminin and fibronectin. In addition, the tumor mass present astrocytes associated to the tumor edge, which display a reactive phenotype when they contact tumor cells. Interestingly, GBM could also induce EMT-like in reactive astrocytes, through the release of several extracellular molecules, ranging from growth factors to cytokines and chemokines. Tumor-associated reactive astrocytes, in turn, interact with glioma cells and facilitate the progression, survival and aggression of tumors by releasing different molecules, forming a positive-feedback with tumor cells.
Glioblastoma (GBM), cancer-associated fibroblast (CAF), extracellular matrix (ECM), insulin growth factor (IGF), stromal cell-derived factor 1 (SDF-1), metalloproteinases (MMPs), transforming growth factor β (TGF- β), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), connective tissue growth factor (CTGF), interleukin-6 (IL-6), epidermal growth factor (EGF), Zinc finger E-box-binding homeobox 1 (ZEB1), zinc finger protein SNAI2 (Slug), zinc finger protein SNAI1 (Snail), secreted protein acidic and rich in cysteine (SPARC).

6. Conclusions

This present study indicated that reactive astrocytes associated to tumor mass undergo EMT-like, thereby supporting tumor progression by inducing invasion and migration. In turn, GBM cells would be able to induce more astrogliosis and EMT, providing a feedback that favors tumor growth. More studies are required to validate our theory and to better understand the regulation that guide interactions between GBM and astrocytes.

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Conflicts of interest

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuint.2018.11.016.

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