Editorial: Epithelial to Mesenchymal Plasticity in Colorectal Cancer

Federico Bocci1,2, Regine Schneider-Stock3,4 and Sreeparna Banerjee5*

1NSF-Simons Center for Multiscale Cell Fate Research, Irvine, CA, United States, 2Department of Mathematics, University of California, Irvine, Irvine, CA, United States, 3Experimental Tumorpathology, Institute of Pathology, Universitätsklinikum, Erlangen, Germany, 4Comprehensive Cancer Center-EMN (CCC), Friedrich-Alexander University Erlangen, Erlangen, Germany, 5Department of Biological Sciences, Middle East Technical University, Ankara, Turkey

Keywords: EMT, colorectal cancer, plasticity, partial EMT, MET

Editorial on the Research Topic

Epithelial to Mesenchymal Plasticity in Colorectal Cancer

Epithelial-mesenchymal transition (EMT) is a core cellular program in vertebrate embryonic development where the expression of key junctional and cytoskeletal proteins such as E-Cadherin and Vimentin orchestrate stages of embryogenesis such as gastrulation or morphogenesis (Kalluri and Weinberg, 2009; Hanahan and Weinberg, 2011). In 2003, EMT was linked to carcinogenesis (Yang et al., 2020) leading to extraordinary interest in understanding the molecular basis of EMT in cancer.

When epithelial tumors progress, they lose cell–cell contacts and apico–basal polarity, transforming into spindle-shaped mesenchymal structures. Such cells also gain capabilities of motility and invasiveness for metastasis (Dongre and Weinberg, 2019). At metastatic sites these cells can revert to an epithelial state to proliferate and generate secondary metastases, a process defined as mesenchymal–epithelial transition (MET). Due to this ability to undergo both EMT and MET, tumor cells can also exist in a number of intermediate states, the so called epithelial/mesenchymal hybrid phenotypes contributing to epithelial to mesenchymal plasticity (EMP) (Saitoh, 2018). Such cells maintain cell-cell contact to disseminate as circulating tumor cells (CTC) (Jolly et al., 2015). Although single cell CTCs appear to be more predominant, clustered CTCs (also known as microemboli) are associated with more efficient metastatic spread and worse prognosis in most carcinomas (Mizukoshi et al., 2020; Semaan et al., 2021). E-cadherin is gained in these cells; however, such collective migration is thought to reflect intermediate EMT.

EMT proteins can have various non-EMT related functions and act in a tissue-specific manner such as acquisition of immunosuppression and cancer stem cell (CSC)-like features (Mani et al., 2008; Saitoh, 2018). The tumor-associated reactive stroma is also known to actively regulate the expression of EMT genes (Dongre and Weinberg, 2019) and thereby promote tumor progression and metastasis. In this special issue, Vuletic et al. review the role of Natural Killer (NK) cells in the process of EMT (Vuletic et al.). EMT-associated gain of NK cell ligands in cancer cells may enhance NK cell mediated cytotoxicity, whereas an immune suppressive tumor microenvironment (TME) may activate enzymes that lead to a loss of ligands. He et al. show in this special issue that PSMC5 altered the type of immune cells in the TME of CRC by suppressing the infiltration of CD8+ T cells and enhancing the infiltration of innate immune cells such as macrophages and neutrophils and was associated with EMT (He et al.).

EMT may enhance chemoresistance with evidence for enhanced drug efflux, slower cell proliferation and avoiding apoptosis signaling pathways. Slug was implicated in the development of partial EMT and resistance to doxorubicin via upregulation of drug efflux transporters and stemness in liver cancer cell lines (Karaosmanoglu et al., 2018). Yu et al. show in this special issue that
Vitamin D3 can enhance the sensitization of CRC cells to ionizing radiation via the expression of cystatin D and plasminogen activator inhibitor-1 (PAI-1) and by reversing EMT (Yu et al.). Song et al. show that expression of β-arrestin1 enhanced the motility of CRC cells via the activation of Wingless/integration-1 (Wnt)/β-catenin signaling (Song et al.).

Reliance on one or two genes to evaluate a process as complex as EMT as well as the use of acute tumor models may not be sufficient to recapitulate the heterogeneity, metabolic idiosyncrasies, and growth pattern of a slow growing tumor (Wang et al., 2016). Over the last decade, integrating experimental investigations with theoretical and computational modeling have helped uncover the dynamics of EMT and characterize intermediate epithelial/mesenchymal cell states. These approaches have been able to provide significant clinical insights by predicting critical molecular players and interventions and their effect on the stability of highly aggressive intermediate E/M phenotypes (Steinway et al., 2015; Bocci et al., 2019b). The rapid expansion of single cell transcriptomics has also brought forth integrated approaches to identify intermediate states along EMT trajectories (Sha et al., 2020; Sacchetti et al., 2021), reconstruct core gene regulatory networks (Ramirez et al., 2020), and study intra- and intercellular signaling dynamics during EMT (Bocci et al., 2021). While these methods have provided invaluable insights, many challenges lie ahead that will benefit from the integration of experimental investigation with theoretical and computational analysis.

A first area of investigation relates to the connection between EMT and other axes of cancer progression, such as initiation, resistance to therapies, tumor-immune system interactions and metabolism. Mathematical models of the underlying interconnected regulatory networks suggest that hybrid epithelial/mesenchymal cancer cells exhibit a high phenotypic plasticity that enables stem-like properties (Bocci et al., 2019a). Using modeling experiments, Jia et al. report in this special issue that NRF2 mediated epigenetic regulation of the expression of Snail can stabilize a cell in the state of partial EMT, preventing it from transitioning to a complete mesenchymal state (Jia et al.). Moreover, modeling experiments suggest that partial EMT can facilitate hybrid metabolic states with combination of glycolysis and oxidative phosphorylation, contrary to primary tumors that mostly rely on glycolysis (Jia D. et al., 2021). These findings need to be supported by robust in vivo data in order to identify metabolic vulnerabilities that can be targeted for therapy.

A second open area of investigation concerns the integration of biochemical and biophysical aspects of EMT. While the models discussed above adopt a “systems-biology” approach that focuses primarily on the intracellular circuitry at the bases on EMT regulation, cells undergoing EMT modify their mechanical properties by regulating their adhesion, polarity, and cytoskeletal structure (Dongre and Weinberg, 2019), suggesting the possibility of high heterogeneity. Adding to this complexity, the regulation of EMT depends on the interplay between tumor cells and their local microenvironment, for instance by regulating the ability of leader cancer cells to ease the passage of follower cells through the extracellular matrix (Mercedes et al., 2021). Therefore, cancer cell migration and invasion rely on better understanding of the intricate mechanochemical feedback between cancer cells and their microenvironment.

This special issue on “Epithelial to Mesenchymal Plasticity in Colorectal Cancer” explores the complex ramifications of these themes with a specific focus on colorectal cancer (CRC). The results reported provide new insights into EMT plasticity and its implications in CRC.

**REFERENCES**

Bocci, F., Levine, H., Onuchic, J. N., and Jolly, M. K. (2019a). Deciphering the Dynamics of Epithelial-Mesenchymal Transition and Cancer Stem Cells in Tumor Progression. *Curr. Stem Cell Rep.* 5, 11–21. doi:10.1007/s40778-019-0105-3

Bocci, F., Tripathi, S. C., Vilchez Mercedes, S. A., George, J. T., Casabar, J. P., Wong, P. K., et al. (2019b). NRF2 Activates a Partial Epithelial-Mesenchymal Transition and Is Maximally Present in a Hybrid Epithelial/Mesenchymal Phenotype. *Integr. Biol.* 11, 251–263. doi:10.1039/mh20y2021

Bocci, F., Zhou, P., and Nie, Q. (2021). Single-Cell RNA-Seq Analysis Reveals the Acquisition of Cancer Stem Traits and Increase of Cell-Cell Signaling during EMT Progression. *Cancers* 13, 5726. doi:10.3390/cancers13225726

Dongre, A., and Weinberg, R. A. (2019). New Insights into the Mechanisms of Epithelial-Mesenchymal Transition and Implications for Cancer. *Nat. Rev. Mol. Cell Biol.* 20, 69–84. doi:10.1038/s41580-018-0080-4

Hanahan, D., and Weinberg, R. A. (2011). Hallmarks of Cancer: The Next Generation. *Cell* 144, 646–674. doi:10.1016/j.cell.2011.02.013

Jia, D., Park, J. H., Kaur, H., Jung, K. H., Yang, S., Tripathi, S., et al. (2021a). Towards Decoding the Coupled Decision-Making of Metabolism and Epithelial-To-Mesenchymal Transition in Cancer. *Br. J. Cancer* 124, 1902–1911. doi:10.1038/s41416-021-01385-y

Jia, D., Park, J. H., Kaur, H., Jung, K. H., Yang, S., Tripathi, S., et al. (2021b). Decoding Leader Cells in Collective Cancer Invasion. *Nat. Rev. Cancer* 21, 592–604. doi:10.1038/s41568-021-00376-8

Kalluri, R., and Weinberg, R. A. (2009). The Basics of Epithelial-Mesenchymal Transition. *J. Clin. Invest.* 119, 1420–1428. doi:10.1172/JCI39104

Karasmanoglu, O., Banerjee, S., and Sivas, H. (2018). Identification of Biomarkers Associated with Partial Epithelial to Mesenchymal Transition in the Secretome of Slug Over-expressing Hepatocellular Carcinoma Cells. *Cell Oncol.* 41, 439–453. doi:10.1007/s13402-018-0384-6

Jolly, M. K., Boareto, M., Huang, B., Jia, D., Lu, M., Ben-Jacob, E., et al. (2015). Implications of the Hybrid Epithelial/Mesenchymal Phenotype in Metastasis. *Front. Oncol.* 5. 155. doi:10.3389/fonc.2015.00155

Mercedes, S. A. V., Bocci, F., Levine, H., Onuchic, J. N., Jolly, M. K., and Wong, P. K. (2021). Decoding Leader Cells in Collective Cancer Invasion. *Nat. Rev. Cancer* 21, 592–604. doi:10.1038/s41568-021-00376-8

Mizukoshi, K., Okazawa, Y., Haeno, H., Koyama, Y., Sulidan, K., Komiyama, H., et al. (2021). Metastatic Seeding of Human Colon Cancer Cell Clusters Expressing the Hybrid Epithelial/mesenchymal State. *Int. J. cancer* 146, 2547–2562. doi:10.1002/ijc.32672

Ramirez, D., Kohar, V., and Lu, M. (2020). Toward Modeling Context-specific EMT Regulatory Networks Using Temporal Single Cell RNA-Seq Data. *Front. Mol. Biosci.* 7, 54. doi:10.3389/fmolb.2020.00054

**AUTHOR CONTRIBUTIONS**

FB, RS-S and SB drafted the editorial with equal contribution.

Frontiers in Cell and Developmental Biology | www.frontiersin.org 2 June 2022 | Volume 10 | Article 950980
Sacchetti, A., Teeuwen, M., Verhagen, M., Joosten, R., Xu, T., Stabile, R., et al. (2021). Phenotypic Plasticity Underlies Local Invasion and Distant Metastasis in Colon Cancer. *Elife* 10. doi:10.7554/eLife.61461

Saitoh, M. (2018). Involvement of Partial EMT in Cancer Progression. *J. Biochem.* 164, 257–264. doi:10.1093/jb/mvy047

Semaan, A., Bernard, V., Kim, D. U., Lee, J. J., Huang, J., Kamyabi, N., et al. (2021). Characterisation of Circulating Tumour Cell Phenotypes Identifies a Partial-EMT Sub-population for Clinical Stratification of Pancreatic Cancer. *Br. J. Cancer* 124, 1970–1977. doi:10.1038/s41416-021-01350-9

Sha, Y., Wang, S., Zhou, P., and Nie, Q. (2020). Inference and Multiscale Model of Epithelial-To-Mesenchymal Transition via Single-Cell Transcriptomic Data. *Nucleic Acids Res.* 48, 9505–9520. doi:10.1093/nar/gkaa725

Steinway, S. N., Zañudo, J. G. T., Michel, P. J., Feith, D. J., Loughran, T. P., and Albert, R. (2015). Combinatorial Interventions Inhibit TGFβ-Driven Epithelial-To-Mesenchymal Transition and Support Hybrid Cellular Phenotypes. *npj Syst. Biol. Appl.* 1, 15014. doi:10.1038/npj巴萨.2015.14

Wang, J., Wei, Q., Wang, X., Tang, S., Liu, H., Zhang, F., et al. (2016). Transition to Resistance: An Unexpected Role of the EMT in Cancer Chemoresistance. *Genes Dis.* 3, 3–6. doi:10.1016/j.gendis.2016.01.002

Yang, J., Antin, P., Berx, G., Blanpain, C., Brabletz, T., Bronner, M., et al. (2020). Guidelines and Definitions for Research on Epithelial-Mesenchymal Transition. *Nat. Rev. Mol. Cell Biol.* 21, 341–352. doi:10.1038/s41580-020-0237-9

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Bocci, Schneider-Stock and Banerjee. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.