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Current Opinion in Systems Biology

Computational systems biology of epithelial-hybrid-mesenchymal transitions

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Abstract

Metastasis accounts for more than 90% of cancer-related deaths, and is fueled by fine-tuned transitions among many cellular phenotypes. Transitions among epithelial (strong cell–cell adhesion, no or little migration), mesenchymal (no cell–cell adhesion, high migration), and hybrid epithelial/mesenchymal (both cell–cell adhesion and cell migration) phenotypes are considered to be a hallmark of metastasis. Recent years have witnessed rapid progress in mapping the regulatory networks underlying these transitions. This progress has enabled the capability to develop computational systems biology models to characterize how various intracellular and extracellular signals can drive these transitions. Here, we discuss how different mathematical models have contributed to elucidating the underlying principles of these transitions and guided further experiments to address key unanswered questions concerning metastasis.

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Current Opinion in Systems Biology 2017, **3**:1–6

This review comes from a themed issue on **3: Mathematical modelling (2017)**

Edited by **Martin Falcke**

For a complete overview see the Issue and the Editorial

Available online 17 February 2017

http://dx.doi.org/10.1016/j.coisb.2017.02.004

Keywords

Metastasis, Epithelial–mesenchymal plasticity, Hybrid epithelial/mesenchymal, Cancer stem cells, Computational modeling.

Introduction

Metastasis causes above 90% of all cancer-related deaths. Metastasis involves primary tumor cells leaving the home organ, entering the bloodstream, disseminating throughout the body, and forming secondary tumors (metastases) at distant organs [1]. The 'metastatic cascade' is extremely challenging for cancer cells. Therefore, only 0.01% of cells entering the circulation are estimated to be able to form metastases [2].

An intriguing aspect of metastasis emerges from the fact that more than 80% of cancers are carcinomas, i.e. cancers beginning in epithelial organs such as breast, prostate, and lung. Carcinoma cells adhere tightly to their neighbors in highly organized 3-D structures and lack the innate ability to invade surrounding tissue. Standard thinking in the field suggests that to metastasize, the cells shed some epithelial traits of cell polarity and E-cadherin based cell—cell adhesion, and pick up mesenchymal features of migration and invasion [3–5]. After reaching the distant organ, these migratory cells often lose migration and regain cell—cell adhesion, reverting to an epithelial phenotype. Thus, in many cases, these reversible bidirectional transitions among epithelial and mesenchymal phenotypes – EMT (Epithelial—Mesenchymal Transition) and its reverse MET (Mesenchymal—Epithelial Transition) – form the cornerstone of cancer metastasis [6]. We would be remiss in not mentioning the raging controversy within the EMT field regarding recent claims that EMT is dispensable for metastasis but required for emergence of drug resistance [7,8]. These recent reports have raised important issues such as whether these results hold true only for specific genetically engineered mouse models (GEMMs), whether the markers used are truly indicative of EMT, and whether the knockdown of one transcription factor ablated EMT fully [2,9].

Recent experimental and computational studies have suggested that these transitions are rarely 'all-or-none', instead cells can exhibit a spectrum of intermediate or hybrid epithelial/mesenchymal (E/M) phenotypes [10–17]. Such hybrid E/M cells can both adhere to their neighbors and migrate, thereby leading to tumor budding and/or clustered migration of Circulating Tumor Cells (CTCs) [18,19]. These clusters, although quite rare, can form up to 50-times more secondary tumors as compared to individually migrating CTCs, suggesting the enhanced metastatic potential of a hybrid E/M phenotype [20,21]. Furthermore, the presence of clusters in patients can predict poor survival [20]. Therefore, understanding how cells transition among epithelial, mesenchymal and hybrid E/M phenotypes can offer novel insights into halting metastatic progression.

Regulatory networks underlying EMT/MET

EMT can be induced by many signaling pathways such as TGFβ, HGF, EGF, FGF, Wnt, Notch, NF-kB,

Hedgehog, JAK/STAT, and Hippo [22], hypoxia [23], and mechanical factors such as extracellular matrix (ECM) density [24]. These signals often activate one or more of EMT-inducing transcription factors (EMT-TFs) such as ZEB1/2, SNAIL1/2, TWIST1, Goosecoid — all of which can, directly or indirectly, repress epithelial genes including E-cadherin — the inhibition of which is considered as a hallmark of EMT [22]. Besides transcriptional control, EMT and MET can also be regulated by microRNA-mediated translational regulation, alternative splicing of mRNAs, and epigenetic modifiers [25–27]. For instance, ZEB1/2 directly bind to miR-200 promoters and repress their expression, and miR-200 can bind to 3′ UTR of mRNA of ZEB1/2 and prevent translation [27]. Similarly, ZEB1 can repress ESRP1 (Epithelial Splicing Regulatory Protein 1) that governs alternative splicing of multiple mRNAs, some of which can feedback to control ZEB1 levels [26]. Multiple such feedback loops can fine-tune cellular plasticity and allow for the existence of intermediate phenotype(s) [28].

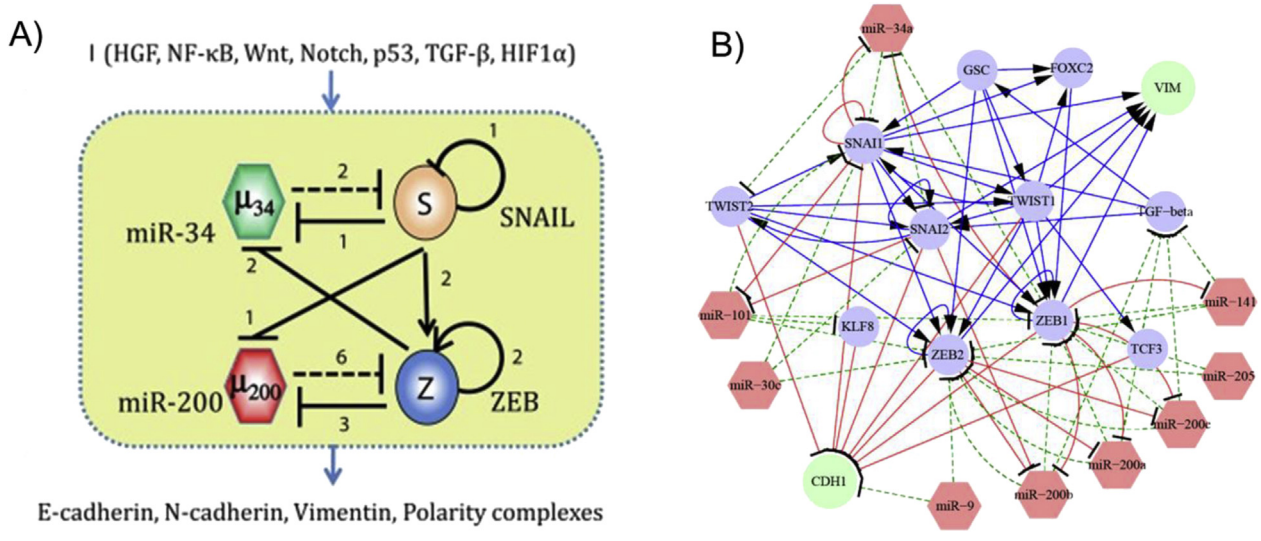
Deciphering these multiple layers of control of epithelial-hybrid-mesenchymal transitions, coupled with high-throughput data collection at gene expression, protein, and epigenetic levels, has driven a surging interest in developing many systems biology models that can capture the underlying principles of cellular plasticity and its contribution to metastasis. Various mathematical models — both from a mechanism-driven 'bottom-up' and a data-driven 'top-down' perspective — have been developed recently that offer insights into the dynamics, stability, reversibility and heterogeneity of these transitions.

Mechanism-driven 'bottom-up' models of EMT

Mechanism-based 'bottom-up' models represent experimentally identified interactions among a set of small number of core players that regulate EMT/MET, and characterize the emergent dynamics of the regulatory network. The first two 'bottom-up' attempts to model EMT focus on interactions between two microRNA families miR-34, miR-200 and two EMT-TF families ZEB and SNAIL [10,11]. These small-scale models capture the kinetics of individual reactions in the network, i.e. similar to the aforementioned miR-200/ZEB mutually inhibitory loop, miR-34 and SNAIL mutually inhibit each other, although with different strengths of inhibition [29–32] (Figure 1A).

Two recent works [10,11] demonstrate that this core network can allow for the existence of a hybrid E/M or partial EMT phenotype, in addition to the epithelial (E) and mesenchymal (M) phenotypes. Also, they predicted a co-existence of multiple phenotypes, a prediction that was validated in many follow-up experimental studies illustrating subpopulations of E, hybrid E/M and M cells in varying ratios in multiple cancer cell lines [16,33]. A key difference in predictions of both models related to the levels of ZEB in hybrid E/M cells — while Tian *et al.* [11] hypothesize that both miR-34/SNAIL and miR-200/ZEB act as bistable switches and that hybrid E/M cells are (high SNAIL, low ZEB), Lu *et al.* [10] propose that miR-200/ZEB feedback loop acts as a tristable switch and that hybrid E/M cells have (medium miR-200, medium ZEB) levels. The different results for hybrid E/M phenotype emerge from different modeling assumptions. For instance, Tian *et al.* [11] assume simple

Figure 1



Overview of 'bottom-up' mechanism-driven models of EMT. A) Small-scale network model of EMT comprising few core players focused on kinetics of individual reactions (adapted from Ref. [19]), **B**) Large-scale network model of EMT focused more on the topology of the network than the kinetics of individual reactions (adapted from Ref. [60]).