Elucidating the design principles of regulatory networks driving cellular decision-making has fundamental implications in mapping and eventually controlling cell-fate decisions. Despite being complex, these regulatory networks often only give rise to a few phenotypes. This project aims to identify the design principles in the regulatory networks underlying these cell-fate decisions that limit the number of phenotypes. Here, we demonstrate that five different networks of varying sizes governing epithelial-mesenchymal plasticity – a process of cell-fate decision with significant impact in cancer metastasis – comprised of two "teams" of players – one comprised of canonical drivers of epithelial phenotype and the other containing the mesenchymal inducers. These "teams" are specific to the topology of these regulatory networks (i.e., are lost when the connections in these networks are shuffled) and orchestrate a bimodal phenotypic landscape with the epithelial and mesenchymal phenotypes being more frequent and dynamically robust to perturbations, relative to the intermediary/hybrid epithelial/ mesenchymal (E/M) ones. The hybrid E/M phenotypes have been demonstrated to enhance the metastatic potential of cancer cells to undergo metastasis. As teams weaken, the incidence of hybrid (E/M) phenotypes increases, making the strengthening of teams a possible mechanism to reduce metastasis. Our analysis reveals that network topology alone can contain information about corresponding phenotypic distributions, thus obviating the need to simulate them. We propose "teams" of nodes as a network design principle that can drive cell-fate canalization in diverse decision-making processes.

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