Population Dynamics of Epithelial-Mesenchymal Heterogeneity in Cancer Cells

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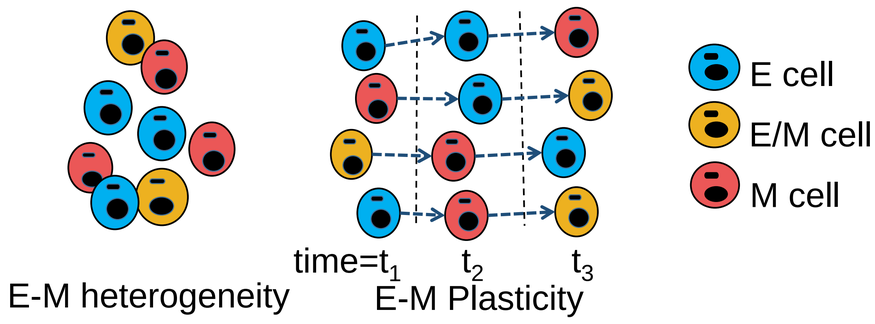
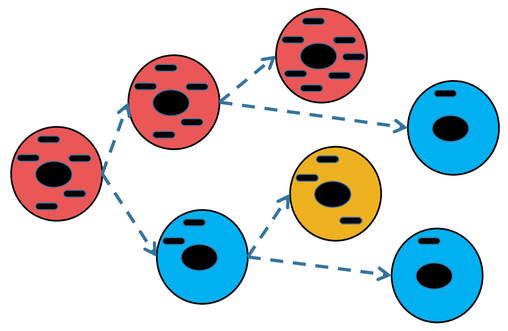
Epithelial-Mesenchymal Heterogeneity and Plasticity

- A cancer cell attain an epithelial (E), mesenchymal (M), or possible intermediate hybrid E/M phenotype based upon its intracellular and extracellular factors.
- Also, stochastic cellular events and changing microenvironment cause cells to switch their phenotypes along E-M axis.
- The E-M heterogeneity has been implicated with cancer metastasis, drug resistance, and immune evasion.
- Thus, mechanistically understanding how E-M subpopulations evolve under various intracellular and extracellular factors can help develop better therapeutic strategies.

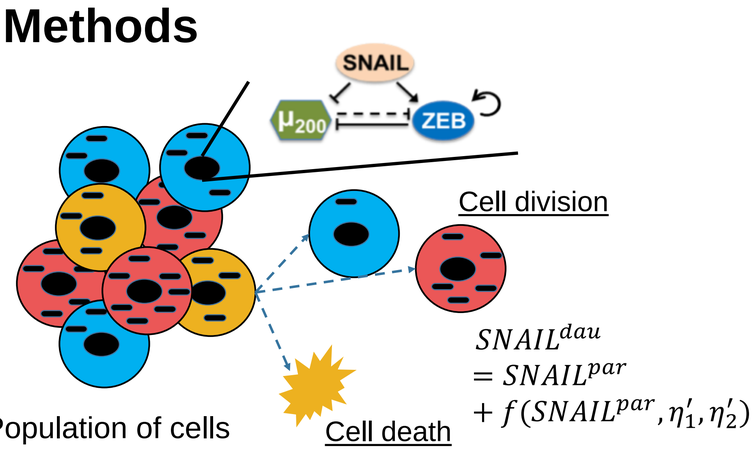


Spontaneous phenotypic switching due to asymmetric cell division

- E-M plasticity can be spontaneous [1] and thus, points us to the inherent stochastic nature of cellular events as it underlying cause.
- Of the many stochastic event that happens in and around cells, we consider here asymmetric cell division as a source of heterogeneity.

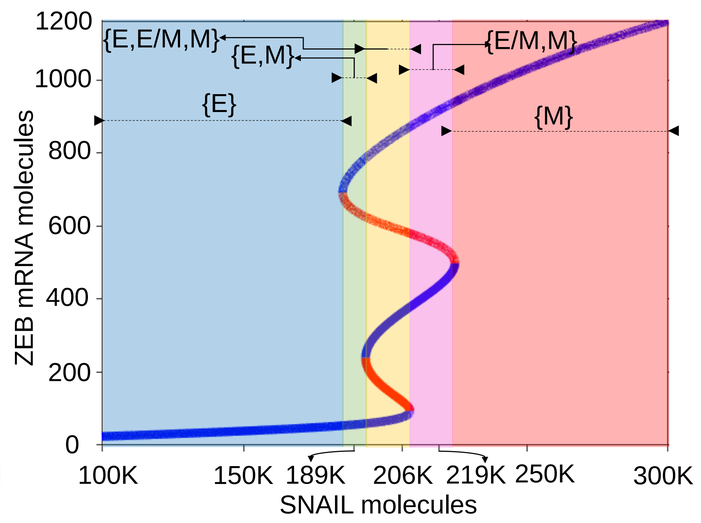


Methods



$$SNAIL^{dau} = SNAIL^{par} + f(SNAIL^{par}, \eta_1', \eta_2')$$

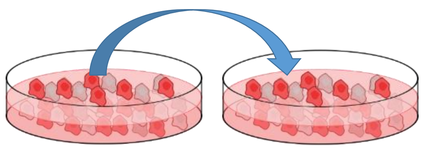
Where,
par : parent, dau : daughter
η_1': Stochastic scaling factor for SNAIL molecules' duplication
η_2': Stochastic scaling factor for SNAIL molecules' partitioning



$$r^{phen} = r_0^{phen} N^{phen} (1 - \frac{N_{tot}}{K})$$

$$d^{phen} = d_0^{phen} N^{phen}$$

Where,
$phen$: E, E/M , M
r^{phen}: doubling rate
d^{phen}: death rate
r_0^{phen}: per capita doubling rate
d_0^{phen}: per capita death rate
N : cell count
tot: total cells
K : Carrying capacity



Passaging on 80% confluency (Sampling 10% of cells when population size is above 80% of carrying capacity)

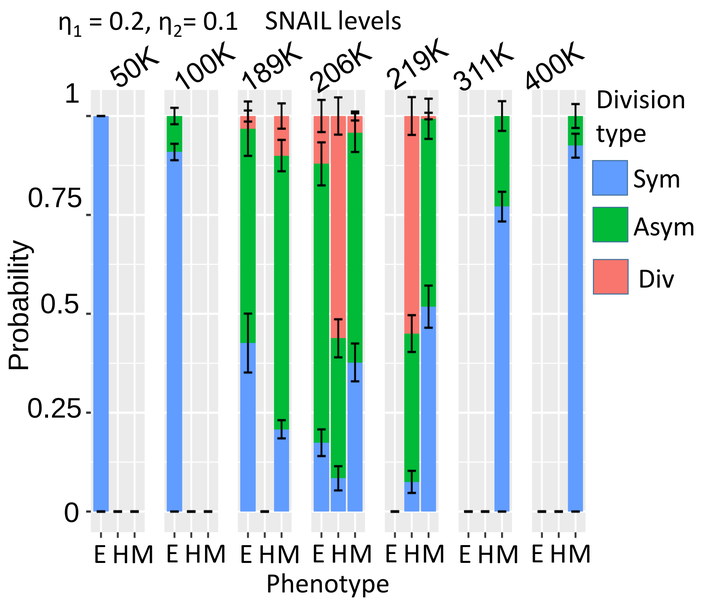
Results

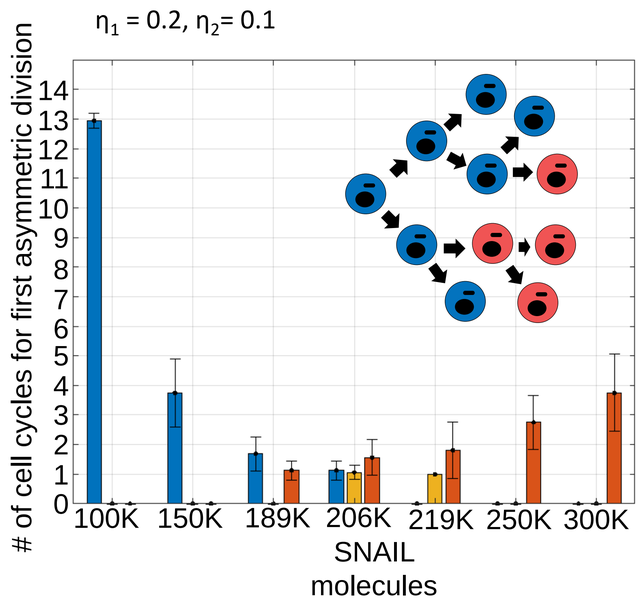
Different initial fractions of cells converge to High E and low M distribution pattern

DT 20 hrs, η_1 = 0.2, η_2 = 0.1. Initial population size = 200

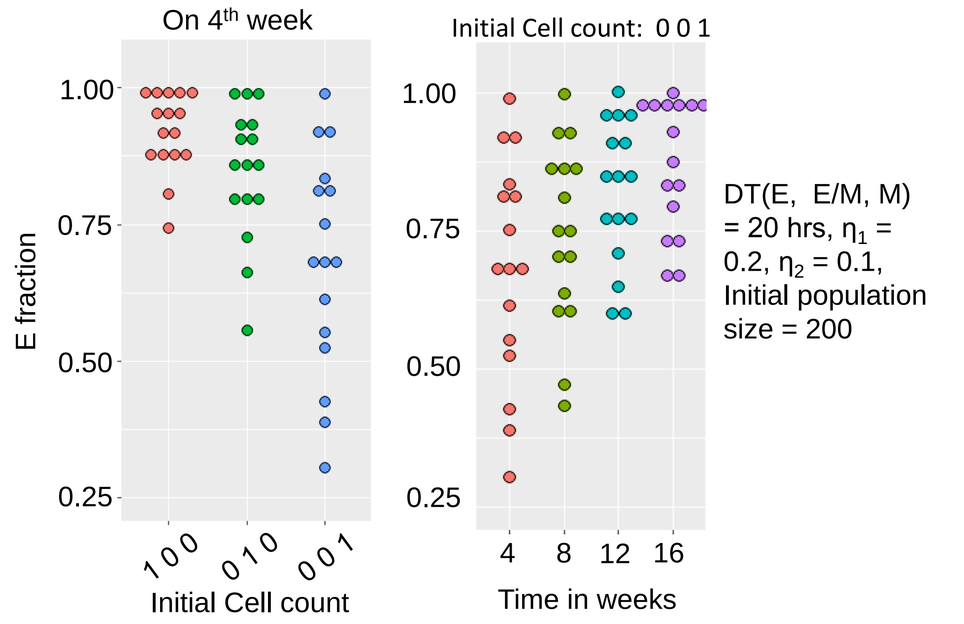
Doubling time (DT) and noise levels determines rate of convergence to High E and low M phenotype distribution

Asymmetric division probabilities and rates of a cell depends on its location on E-M axis





High variability in E to M phenotype fraction among single cell clones in initial weeks of time



DT(E, E/M, M) = 20 hrs, η_1 = 0.2, η_2 = 0.1, Initial population size = 200

Conclusions

Asymmetric cell division, with stochastic fluctuations in daughter cells' SNAIL levels proportional to the dividing parent levels, lead to dominance of E phenotype in the population. Thus, it can be one possible mechanism leading to high $EpCAM^{high}$ (Epithelial phenotype) and low $EpCAM^{low}$ (Mesenchymal phenotype) distribution observed in PMA42-LA breast cancer cells[2]. Moreover, the variability in EpCAM distribution among single cell clones is also being captured[2].

Future Direction

- Study regulatory mechanism involved in asymmetric cell division to separate the regulatory and stochastic components of it.
- Study the role of PSFs, epigenetic and non-cell autonomous factors in modulating the population's phenotypic distribution.

Acknowledgment

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Selected references

[1]. Ruscetti M et al. HDAC inhibition impedes epithelial-mesenchymal plasticity and suppresses metastatic, castration resistant prostate cancer. Oncogene. 2016; 35(29):3781-3795. https://doi.org/10.1038/onc.2015.444. PMID: 26640144
[2]. Bhatia S, Monkman J, Blick T, Pinto C, Waltham M, Nagaraj SH, Thompson EW. Interrogation of Phenotypic Plasticity between Epithelial and Mesenchymal States in Breast Cancer. J Clin Med. 2019; 8: 893. https://doi.org/10.3390/jcm8060893 PMID: 31234417