Design principles of regulatory networks driving phenotypic plasticity in cancer

PhD admissions | Jan 2023

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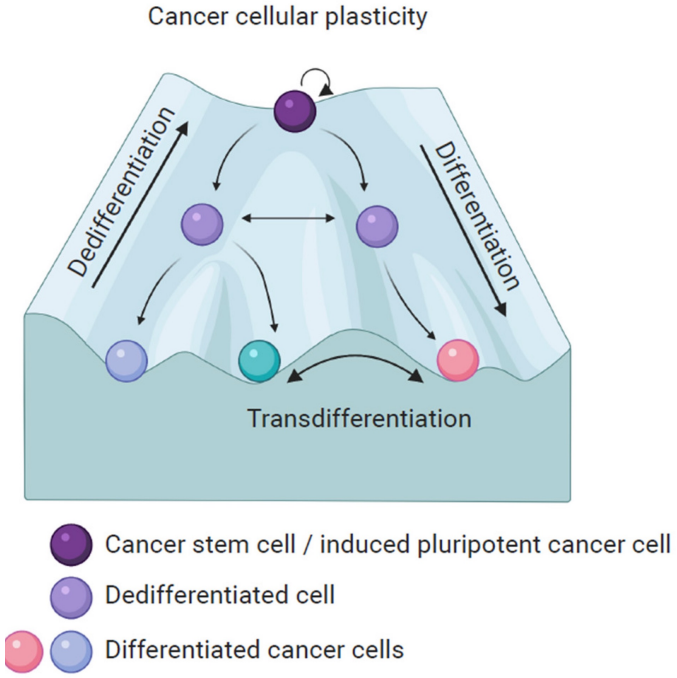
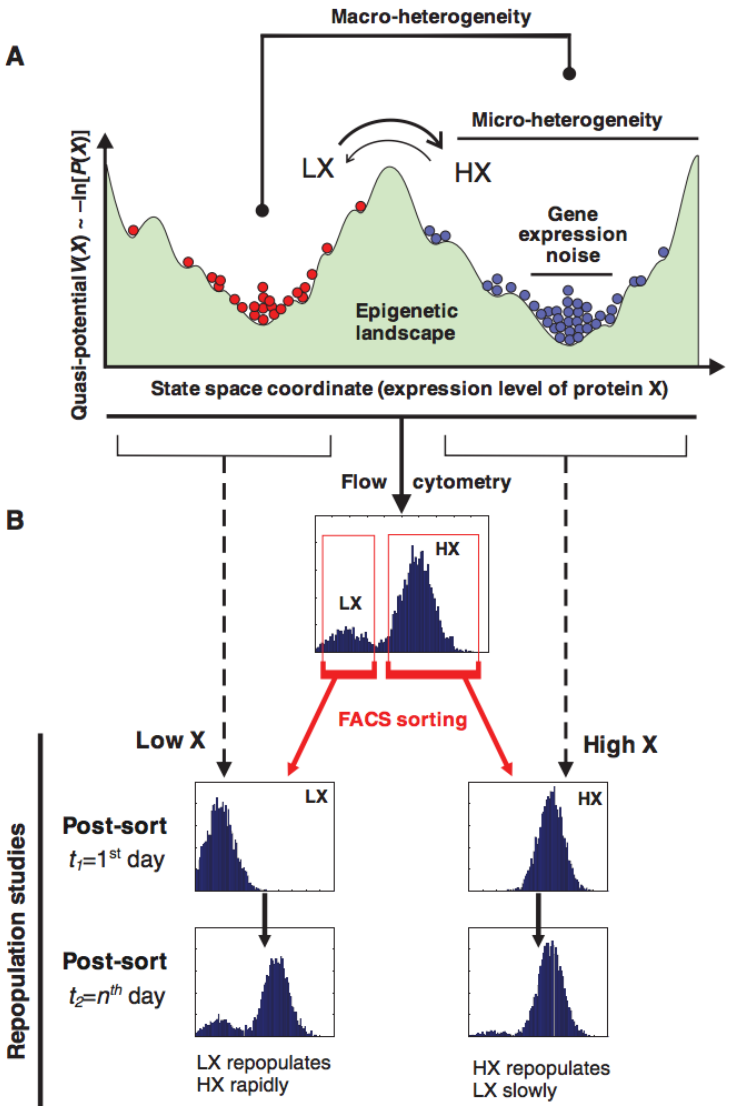
Phenotypic plasticity and non-genetic heterogeneity

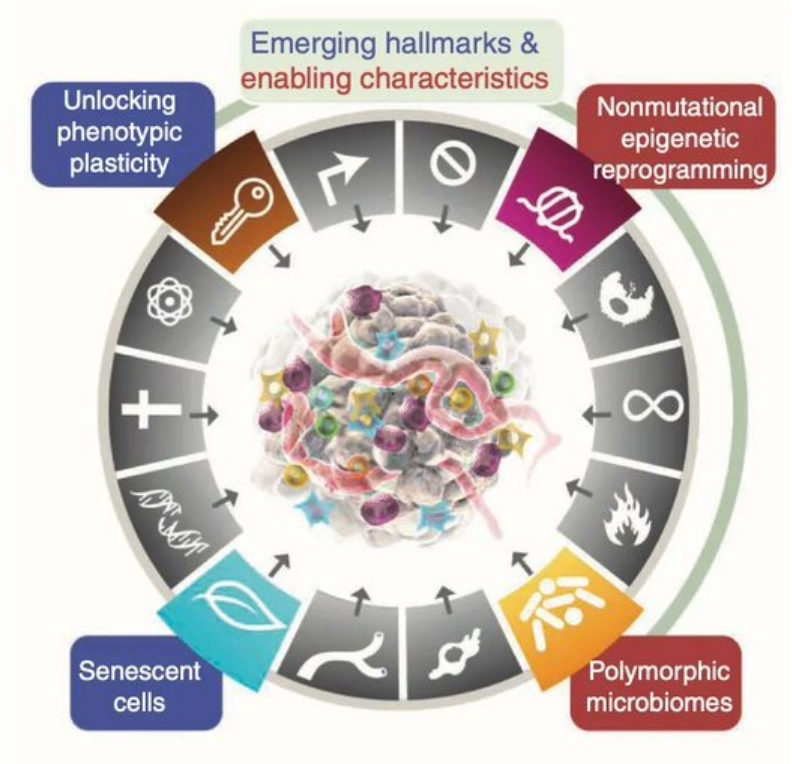
Cellular/Phenotypic plasticity: Ability of cells to switch their phenotype/behavior reversibly in response to environmental conditions





Huang *et al.* Development 2009
Granados *et al.* Int J Mol Sci 2020

Cellular plasticity: a hallmark of cancer



Hanahan, Cancer Discovery 2022

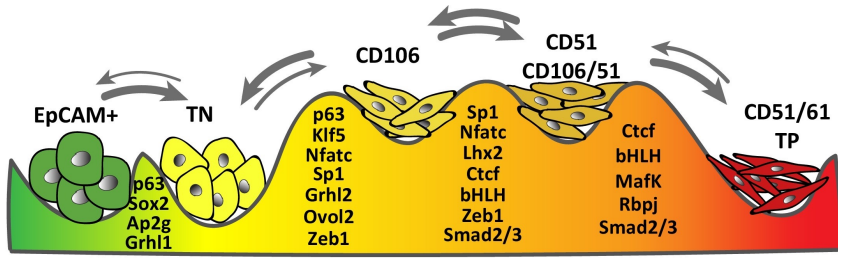
- Cancer cells exhibit plasticity along multiple axes, such as:

  - Epithelial-Mesenchymal Plasticity
  - Metabolic reprogramming
  - Cancer Stem Cells

- The dynamics of such plasticity is shaped by underlying complex regulatory networks.

- We need a better understanding of this dynamics to be able to modulate cancer cell plasticity and eventually restrict metastasis.

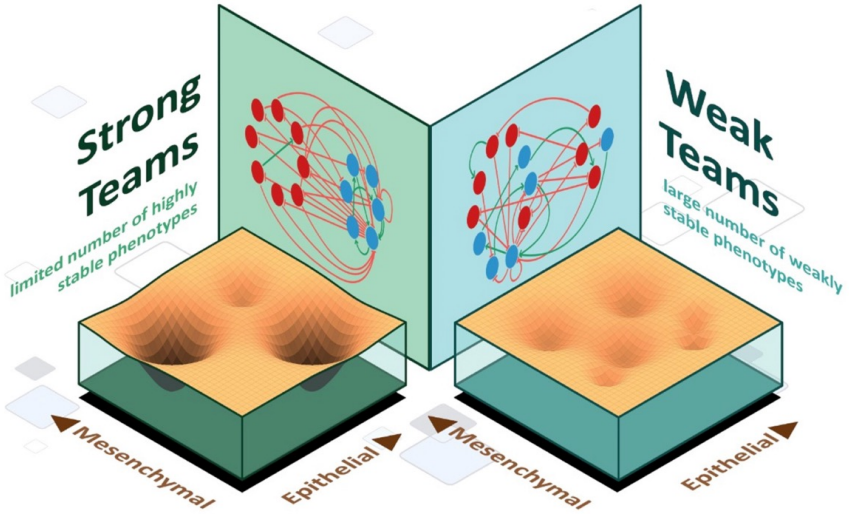
Landscape of epithelial-mesenchymal plasticity



	Epithelial tumor cells	Early hybrid EMT state	Hybrid EMT state	Late hybrid EMT state	Mesenchymal tumor cells
Proliferation	+++++	++++	+++	++	+
Invasion	+	++	+++	++++	+++++
Plasticity	+	++	+++	++++	++
Stemness	+	+++	+++	+++	+++
Metastasis	+	++++	++++	++	+

Experimental data *in vitro* & *in vivo* shows that the hybrid E/M cells are more 'plastic' than the extreme E or M phenotypes.

Pastushenko *et al.* Nature 2019



Network simulations reveal that underlying regulatory network topology (lack of "teams" for hybrid E/M state) can explain the above experimental data.

Hari *et al.* eLife 2022

Questions of interest

Through integrating high-throughput experimental data with mechanism-based (mathematical) models, we will answer the following set of questions:

- Do other networks of cancer cell plasticity comprise “teams”?
- What salient features do “teams” offer to network dynamics?
- How do “teams” behave when embedded in larger regulatory networks?

Tools and techniques used

- Mathematical modeling of biological regulatory networks
- Simulating networks through ODEs and through Boolean logic
- Analyzing experimental high-throughput data (cell lines, tumors)

Required background

- Basic understanding of ODEs and nonlinear dynamics (or the self-driven will to acquire them)
- Keen interest in pursuing interdisciplinary research (i.e. reading literature in systems biology and phenotypic plasticity in cancer)
- **Note:** Students from physics/chemistry/mathematics/engineering background are welcome too, provided they show interest in acquiring the relevant understanding of biology

Further reading

- Hari K.. **Jolly MK** (2022). Landscape of epithelial-mesenchymal plasticity as an emergent property of coordinated modules in regulatory networks. *eLife*, 11*:* e76535
- Harlapur P, Duddu AS, Hari K, **Jolly MK** (2022). Functional resilience of mutually repressing motifs embedded in larger regulatory networks. *bioRxiv*: 475824