Elucidating multiscale mechanisms of cancer cell reprogramming: theory and experiment

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***Short Abstract* — Cell plasticity and invasiveness make it extremely difficult to control cancer metastasis. Surprising evidence suggests metastatic cancer cells may be reprogrammed to a less destructive phenotype in the presence of embryonic signals. However, the molecular mechanisms that underlie the reprogramming process are unclear. Here, we present an integrated theoretical and experimental platform that allows us to evaluate model mechanisms that drive tumor cell reprogramming. We will discuss experimental data on the dynamics of the reprogramming process and produce a simple computational model that describes a mechanistic basis for cancer cell reprogramming to a stable non-metastatic phenotype.**

***Keywords* — cancer, metastasis, plasticity, invasion, reprogramming, embryo, microenvironment, neural crest.**

I. Purpose

A dynamic, complex relationship exists between stem cells and their microenvironment, which plays a pivotal role in cell fate determination – critical to development, wound healing, tissue maintenance, and cancer progression. Key to identifying the molecular mechanisms underlying stem cell plasticity, is understanding the unique epigenetic role of the microenvironment on the emergence of cell phenotype.

Previous studies from our laboratory have revealed the unexpected finding that metastatic human melanoma cells express genes that are associated with multiple cellular phenotypes and their respective precursor cells, the neural crest, suggesting a dedifferentiated, multipotent cancer cell with a plastic phenotype characteristic of stem cells [2,3,4].

Additional evidence supporting the concept of melanoma tumor cell plasticity from our laboratory includes findings that indicate the powerful influence of the chick neural crest-rich microenvironment with respect to reprogramming metastatic melanoma cells to a melanocyte-like phenotype – when exposed to this embryonic milieu [1,3]. Most interestingly, transplanting human metastatic melanoma cells into the neural crest-rich regions of chick embryos show the remarkable ability of the tumor cells to migrate along neural crest pathways resulting in the reprogramming of a subpopulation of melanoma cells induced to re-express melanocyte-like and neuronal-like phenotypes – both derivatives of neural crest cells.

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We aim to elucidate the molecular mechanisms that underlie the reprogramming process that could eventually lead to more effective disease treatment using cell differentiation therapy. Currently, there is no model mechanism that can fully explain how cancer cells regulate their plasticity and invasive ability.

Here, we develop an integrated theoretical and experimental platform using an existing in vivo chick embryo transplant model that permits the visualization of transplanted human tumor cell behaviors and gene expression dynamics. This platform uniquely allows us to generate sets of dynamic measurements of changes in tumor cell plasticity and invasion and evaluate theoretical model predictions that simulate the dynamics of cell reprogramming. We produce a simple computational model that describes the dynamics leading to a stable non-metastatic phenotype.

The ultimate goal is to provide a mechanistic basis for cancer cell reprogramming, based on embryonic NC signals that drive differentiation of highly aggressive melanoma cells and sequester melanoma formation and metastasis[5].

References

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