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TItle:

Beating cancer 'escape room': let's use mathematical modelling to unlock cells!

Abstract:

The inherent capacity of somatic cells to switch their phenotype in response to damage stimuli in vivo might have a pivotal role in ageing and cancer. However, how the mechanisms of phenotype reprogramming are established remains poorly understood. In order to elucidate such mechanisms, we present a stochastic model of combined epigenetic regulation(ER)-gene regulatory network (GRN) to study the plastic phenotypic behaviours driven
by ER heterogeneity. Our analysis of the coupled system reveals the existence of pluripotent stem-like and differentiated steady-states. Crucially, ER heterogeneity of differentiation genes is responsible for conferring
abnormal robustness to pluripotent stem-like states. We then formulate epigenetic heterogeneity-based strategies capable of unlocking and facilitating the transit from differentiation-refractory (pluripotent stem-like) to
differentiation-primed epistates. Our results suggest that epigenetic heterogeneity regulates the mechanisms and kinetics of phenotypic robustness of cell fate reprogramming. The occurrence of tunable switches capable of modifying the nature of cell fate reprogramming from pathological to physiological might pave the way for new therapeutic strategies to regulate reparative reprogramming in ageing and cancer.