Critical State Transitions, Rebellious Cells, and Why it is so Hard to Eradicate Cancer Cells

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Single-cell gene expression analysis affords a new level of resolution for studying cell state dynamics. Cell differentiation into various cell types but also the development of malignant cells are manifestations of cell state dynamics. The ability of a complex gene regulatory network to produce, without mutations, a vast diversity of robust, biologically distinct, inheritable cell states ("attractors") as manifestation of the principle of multi-stability in non-linear dynamical systems, has led to the idea that cancer are cells are trapped in "abnormal attractors" that are not meant to represent physiological cell states. This adds a layer of complication to the standard model of cancer in which Darwinian somatic selection of mutant cells that carry "driver mutations" drive tumor progression. This also means that "cancer without mutations" is in principle possible - as recently found.

We really need to overcome the orthodoxy of a rigid 1:1 mapping between genotype and phenotype in which genetic mutations are the sole agent of permanent and progressing change, and embrace non-genetic phenotypic plasticity, notably, inducible non-genetic state changes in our thinking about tumorigenesis. But to do so properly we need to go beyond hand-waging models and adopt a formal framework.

In this talk I will present the theoretical framework and the experimental findings supporting this thinking. We have formalized non-genetic cell phenotype plasticity as a dynamical system governed by the gene regulatory network. In this framework the distinct, stable biological cell states are attractor states in the high-dimensional gene expression state space. Cancer cells occupy particular ("physiologically forbidden") attractor states, failing to descend to the “normal attractors", and therapy constitutes a perturbation that seeks to push cells out of these cancer attractors into those that represent the apoptotic cell fates. In this formalism a transition between stable attractor states is a symmetry-breaking bifurcation in which the current attractor is destabilized and other attractors become accessible into which the cell will descend. This constitutes a much studied “critical state transition” but in a high-dimensional space. Importantly, in a complex multi-stable system ("rugged epigenetic landscape") destabilization of an attractor also opens up new access to many "hidden" attractor states never intended to be occupied by a cell and even more different from the physiological ones. Now, as the cancer cells exit the cancer attractor during treatment-induced destabilization of their state, not only will they, as desired, move to the target phenotype (the apoptotic state) but: some cells may also "spill" into these newly accessible neighboring attractors which may represent even more stem-like, hence more malignant states. These aberrant non-killed "rebellious cells" triggered by sub-lethal therapy-stress may plant the seed for recurrence. It is in this sense that recurrence of tumors after treatment is not so much described by Darwinian "survival of the fittest" but perhaps more aptly by Nietzsche's principle: "What does not kill me strengthens me". Because of the fundamental need for attractor destabilization in therapy, it is likely that the latter principle widely applies. It does of course not exclude Darwinian selection of genetic mutants -in contrary it facilitates it by enhancing the probability of cells surviving treatment.

Because of the importance of attractor destabilization we developed a tool to detect shifts of cell populations towards bifurcations in which attractors vanish. Indeed, we observed in single-cell resolution measurements of cells undergoing phenotype transitions signatures of postulated critical state transition, as well as the rebellious cells predicted by theory that move into attractors in the opposite direction from that of the desired transition. It follows the general postulate that there is an inherent limitation to any, however selectively targeting cancer drug, as long as it seeks to destabilize the cancerous state. Thus cancer therapy that seeks to kill tumor cells may be more akin to herding cats (than sheep): inherently very difficult.

Friday, Dec 11
11:00am
3305 NSH