Curing Cancer – Part 5 – Key network issues that affect the primary tumor

natpernickshealthblog.wordpress.com/2021/01/17/part-5-key-network-issues-that-affect-the-primary-tumor/

January 17, 2021

17 January 2021

This is my fifth essay about curing cancer based on the principles of complexity theory (follow my blog at **https://natpernickshealthblog.wordpress.com**). This essay discusses key network issues for curative treatment that affect the primary tumor.

1. Kill as many tumor cells as possible. High tumor cell kill is important because: (a) tumor cells directly damage cells, tissue and organ systems, interfering with their physiologic functions which maintain life; (b) tumor cells create an increased workload, both by producing biologic substances that interfere with optimal physiology and by stimulating a response to destroy them; and (c) tumor cells have molecular heterogeneity so killing each tumor cell may destroy a different strategy used by the tumor cell and its progeny to overcome the body's antitumor defenses.

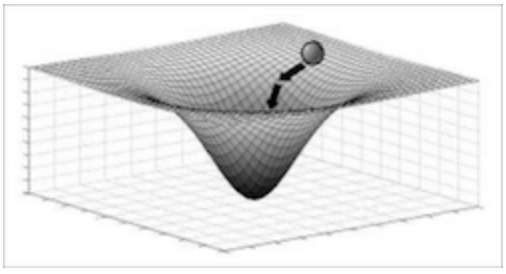
2. Attack multiple targets within local tumor networks. Curative treatment for adult tumors should build on our success in curing cancer in children and young adults, including childhood leukemia, Hodgkin lymphoma and testicular cancer. These cancers are caused by inherited or constitutional cancer predisposition or developmental mutations (**Kentsis 2020**) and exhibit a limited number of somatic (acquired) tumor mutations (**Sweet-Cordero 2019**). Although they typically have no prominent risk factors and show no field effects (widespread premalignant or malignant changes), curative therapy still requires combinations of 3-5 effective treatments, each with different mechanisms of action, mixed and matched for maximum effect **(Mukherjee: The Emperor of All Maladies 2010**). Multiple antitumor agents are necessary because biological pathways are not strictly linear. Rather, they are weblike, allowing cancer cells to bypass important steps blocked by antitumor agents **(Nollmann 2020**, **Ozkan-Dagliyan 2020**). Curing adult cancers may require even more treatment diversity due to: (a) their complex and heterogeneous mutational landscape (**de Sousa 2018**, **Blank 2018**, **Samuel 2011**), (b) the field effects generated by cancer promoters / risk factors acting over decades of exposure and (c) associated systemic network changes that must also be addressed by treatment (to be discussed in the next essay, Part 6).

Drug combinations may be more effective than single agents due to synergy, the interaction of two or more substances producing a combined effect greater than the sum of their separate effects (**Mokhtari 2017**). Determining whether drug combinations are synergistic, additive or antagonistic is time consuming, but "deep learning," other computational approaches and modeling methods may help screen possible combinations for effectiveness (**Kuenzi 2020**, **Sidorov 2019**). Combining different types of therapy may also be effective;

for example, regional hyperthermia combined with radiotherapy may kill cancer stem cells (**Oei 2017**), be synergistic with immune checkpoint inhibitors (**Li 2020**) and improve survival (**Fiorentini 2019**).

3. Move local tumor cell networks into less lethal states. Curative treatment, in addition to killing large numbers of tumor cells through multiple mechanisms, should "normalize" or reduce the malignant traits of tumor cells that survive **(Heudobler 2019**). Fifty years ago, Kauffman discovered that a complex network of thousands of mutually regulating genes in normal cells may produce a stable equilibrium state called an attractor that corresponds to gene expression profiles specific to each cell type (**Kauffman 1969**, **Noble 2015**). Essentially, the environment of biological substances forces them to have similar behavior even though they behave very differently when isolated. Attractors have been analogized to a low energy state or valley on a topographic diagram that pulls in cells with similar network configurations (**Waddington 1957**). See diagrams at **Vallacher 2013**, **Goldberg 2007**.

Attractors maintain cellular network stability against common disruptions in both normal cells and cancer cells. In normal cells, this stability may be disturbed by cancer "super promoters" (risk factors), acting over long time periods, that push cell networks into malignant pathways. In cancer cells, these "cancer attractors" create network stability that makes tumor cells resistant to antitumor treatment (**Huang 2009**, **Pernick 2020**).



Cell attractor pulls different cells into a common configuration

Curative antitumor treatment problems should push tumor cells that survive the treatment towards alternative states with reduced malignant properties. Examples include retinoids for acute promyelocytic leukemia and childhood neuroblastoma (**Nowak 2009**), progestin for endometrial hyperplasia, a premalignant condition (**Gallos 2013**) and other lineage reprogramming agents (**McClellan 2015**, **Gong 2019**). Constant disturbing of parts of the network may also be useful (**Cho 2016, Kim 2017**).

The next essay will discuss key systemic network issues that affect cancer cells by acting outside of the primary tumor.