Curing Cancer – Part 6 – Key systemic network issues

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This is my sixth essay about curing cancer based on the principles of complexity theory. This essay proposes strategies for curative therapy regarding key systemic networks other than those affecting the primary tumor, which were discussed in **Curing Cancer – Part 5**.

1. Disrupt the inflammatory process that plays a central role in promoting and sustaining carcinogenesis. Tumors have been described as wounds that do not heal (**Dvorak 1986**, **Dvorak 2015**). Activation of the inflammatory system, which promotes wound healing and accompanies many malignancies (**Coussens 2002**, **Pernick 2020**), has been considered a major cause of cancer since 1863, when Virchow speculated that some irritants enhance cell proliferation through tissue injury and chronic inflammation (**Schottenfeld 2006**). Inflammation is activated by many cancer risk factors, including excess weight, cigarette smoking, heavy alcohol consumption, aging and a Western diet (high fat, highly processed foods, low consumption of vegetables, fruits and whole grains) (**Antwi 2016**, **Pernick 2020**).

Inflammation may play a central role in promoting carcinogenesis because it is widely connected to other networks and it is unstable because it rapidly initiates sophisticated repair, antimicrobial and antitumor processes. Ultimately, this network instability may propagate to local and systemic networks and promote malignancy (**Morgillo 2018**).

Cancer disrupts the usual coordination of inflammatory networks. Sophisticated biologic processes, such as inflammation and embryogenesis, require coordination of activity, since isolated network activity by itself can be either useful or destructive, depending on its context. For inflammation, this coordination includes triggering both the process and its resolution at the same time (**Serhan 2005**, **Serhan 2020**). As the trauma is repaired or the threat from foreign organisms subsides, the resolution pathways cause networks to revert towards their initial states to prevent bystander damage to tissue (**Sugimoto 2016**). Cancer risk factors may also trigger the inflammatory process but through nonconventional means that do not simultaneously initiate the resolution process (**Fishbein 2020**). This causes persistent inflammation, which may wear down stabilizing factors in inflammatory and adjacent networks, particularly when accompanied by other risk factors, which further drives the malignant process (**Shimizu 2012**, **Huang 2009**).

Curative cancer therapy needs to antagonize or diminish this persistent inflammatory process. Suggested options include: (a) triggering pro-resolution pathways (**Fishbein 2020**, **Park 2020**); (b) using anti-inflammatory agents to diminish inflammation in general

(**Zappavigna 2020, Bruserud 2020**); (c) mimicking the halting mechanisms associated with wound healing (**Shah 2018, Kareva 2016**) and liver regeneration **(Abu Rmilah 2019**); and (d) countering germline (inherited genetic) changes that promote instability in the inflammatory process.

2. Disrupt the microenvironment that nurtures tumor cells at primary and metastatic sites. Cancer risk factors produce a microenvironment that nurtures mutated cells, steers cellular networks towards malignant pathways **(Mbeunkui 2009**), helps them escape immune surveillance (**Labani-Motlagh 2020**) and ultimately promotes invasion by activating cells to mimic physiologic "invasion" of wounded epithelium through the extracellular matrix (**Bleaken 2016, Coussens 2002**). Tumors require a fertile "soil" for the cancer "seeds" to grow (**Fidler 2003**, **Tsai 2014**). For example, Hodgkin Reed-Sternberg cells produce cytokines that assist the survival and proliferation of lymphoma cells (**Wang 2019**) and pancreatic tumor cells produce cytokine IL1β and proinflammatory factors that establish a tumor supportive microenvironment (**Das 2020**, **Huber 2020**). From a network perspective, there is a complex crosstalk among cancer cells, host cells and the extracellular matrix (**Sounni 2013**).

Curative treatment should disrupt or normalize the microenvironment by targeting inflammation, the vasculature and the extracellular matrix (**Mpekris 2020**). For example, anti-VEGF or anti-VEGF receptor treatment can normalize vasculature by reducing vascular permeability (**Gkretsi 2015**). Normalizing the microenvironment may also enhance drug delivery and effectiveness (**Polydorou 2017**, **Stylianopoulos 2018**) or make existing tumors or premalignant states more susceptible to immune system attack (**Ganss 2020**).

It is also important to disrupt the microenvironment of possible metastatic sites. Typically, tumor cells die at secondary sites but the malignant process preconditions the otherwise hostile microenvironment of the secondary site so it can sustain their colonization (**Houg 2018**, **Kaplan 2005**).

3. Disrupt the microenvironment that promotes embryonic features associated with aggressive tumor behavior. In the microenvironment of the fertilized egg, coordinated network activity ultimately moves embryonic related networks towards mature, differentiated phenotypes in the fetus and newborn. However, cancer risk factors stimulate these networks in a non coordinated manner to trigger embryonic properties, such as rapid cell division (**Kermi 2017**), cell migration (**Reig 2014**, **Kurosaka 2008**) and changes to cell differentiation (**Li 2014**) that do not mature over time.

Curative treatment should include agents to promote this maturation, such as retinoids used in acute promyelocytic leukemia (**Madan 2020**), myeloid differentiation promoting cytokines (**McClellan 2015**), cancer cell reprogramming drugs (**Gao 2019**, **Gong 2019**) or possibly agents that halt rapid cell division in embryogenesis (**Kermi 2017**).

4. Repair the immune system dysfunction that coevolves with carcinogenesis. The immune system consists of a web of interacting networks whose effectiveness is systematically degraded with malignant progression. Immune dysfunction in cancer is typically not just the failure of one particular pathway (**Karamitopoulou 2020**). Curative treatment should attempt to improve immune system function with combinatorial therapy that targets multiple aspects of immune dysfunction (**Sodergren 2020**)**.**

5. Promote the activation of gene networks supporting stable, multicellular processes and suppress networks promoting unicellular processes that support malignant type behavior. Multicellular organisms evolved from unicellular organisms by adding new genes and more intricate controls to existing networks for metabolism and replication (**Trigos 2018**, **Trigos 2019**). This enables greater communication and coordination between cells and makes possible higher level functions, such as cell differentiation and programmed cell death (**Trigos 2018**). The new control mechanisms keep cellular and systemic processes on track and shift the survival focus from individual cells towards the organism as a whole (**Davies 2011**). The operation of multicellular and unicellular programs appears to be somewhat mutually exclusive. Inflammation and DNA alterations may damage these multicellular controls, activating the existing genetic toolkit of preprogrammed, malignant behavior in unicellular networks based on what has been described as the atavism hypothesis of cancer (**Davies 2011**, **Trigos 2017**, **Bussey 2017**).

To restore the balance between multicellular and unicellular controls, curative treatment should activate different components of multicellular networks (**Gaponova 2020**, **Hay 1995**). In addition, treatment could target the weaknesses of cancer cells by applying a specific cellular stress that is readily dealt with by healthy cells using evolved capabilities or multicellular programming but not by cancer cells with predominantly unicellular programming (**Lineweaver 2014**). This includes “lethal challenges” of high dose methotrexate with leucovorin rescue (**Howard 2016)** or targeting other aspects of chaotic or unstable states, such as cell-extracellular matrix detachment (**Crawford 2017**).

6. Target the hormones that may promote tumor growth. Physiologic (i.e. normal) levels of estrogens and androgens and elevated levels of insulin are associated with breast **(Dall 2017**), endometrial / uterine (**Rodriguez 2019)**, prostate (**Liu 2020**) and pancreatic cancer (**Andersen 2017, Li 2019, Perry 2020**). The primary mechanism may involve promotion of cell growth, particularly at a stage when these cells are particularly vulnerable to instability.

Simple antagonism of hormonal pathways is possible using tamoxifen for estrogens, antiandrogens for testosterone and metformin for insulin (**Wan 2018)**. One block in these networks is apparently adequate for normalization, in contrast to the 3-5 blocks required for other tumor cell networks. Behavioral changes, such as weight loss, exercise, a healthier diet and reducing alcohol and tobacco use may also be therapeutic by either altering hormone levels or changing their interaction with other risk factors.

7. Antagonize germline changes that promote malignant behavior. Genetic testing of nontumor cells (germline testing) is recommended for all patients with pancreatic cancer (**Stoffel 2019**) and select patients with other cancers or family histories of cancer (**Daly 2020**, **Lincoln 2020**). Results are currently used to determine antitumor therapy (**Zhu 2020**) as well as for cancer screenings, reproductive choices and genetic counseling. We suggest using these results to also provide treatment that: (a) moves premalignant or malignant cells into less harmful pathways as discussed in Part 5; or (b) counters common germline changes in inflammatory, DNA repair, cell cycle stability, immune system or other networks that promote malignancy.

These blog essays have summarized proposed strategies for curative cancer therapy. The next essay will discuss random chronic stress, a newly proposed major factor in how cancer arises that cannot be prevented but can be better understood.