How Cancer Arises from Chronic Inflammation, Based on Complexity Theory

Nat Pernick, M.D., Bingham Farms, Michigan (USA)

Presented at the American Association for Cancer Research (AACR) Virtual Annual Meeting II, June 2020

NatPernick@gmail.com

Introduction

This poster discusses how cancer arises from chronic inflammation based on a complexity theory perspective. We also suggest new insights into its pathophysiology and treatment.

We previously summarized the laws of complexity and self-organization as they relate to cancer (Pernick 2011), and proposed that most adult cancer is due to 9 chronic cellular stressors (Pernick 2017):

* **Chronic inflammation**
* Exposure to carcinogens
* Reproductive hormones (estrogens, androgens)
* Western diet
* Aging
* Radiation
* Immune system dysfunction
* Germ line changes
* Random chronic stress / bad luck

Cancer types associated with chronic Inflammation (see also next column)

* Bladder squamous cell carcinoma (3)
* Cholangiocarcinoma (3)
* Cutaneous squamous cell carcinoma (5)
* Esophageal adenocarcinoma, squamous cell (5, 6)
* Gallbladder cancer (1)
* Gastric carcinoma (1)
* Glioblastoma (7, possibly)
* Hepatocellular carcinoma (6)
* Kaposi sarcoma (2)
* Lymphoma (1, 2, 4, 7)
* Pancreatic adenocarcinoma (6)

* Other weight related carcinomas occur in the breast, colorectum, endometrium and kidney

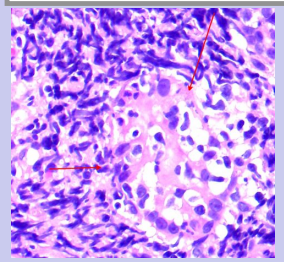
Chronic inflammation etiologies

1. Bacterial infections: *Helicobacter pylori, Salmonella typhi*
2. Viral infections: Hepatitis B / C, HHV8, HTLV-1
3. Parasitic infestations: *Opisthorchis viverrini, Clonorchis sinensis, Schistosoma haematobium*
4. Autoimmunity
5. Trauma including GERD, hot beverages & food
6. Excess weight
7. Immune system dysfunction

Also: diabetes, chronic pancreatitis, COPD
Not discussed: Western diet, aging, immune disorders, germ line variations

Mechanisms of action

* Immune system activation produces reactive oxygen and nitrogen species and nitrosamines
* Tumor immune evasion
* Antigen driven lymphoproliferation
* Continuous mitotic activity due to repair
* Synergy with other chronic stressors
* Creation of a tumor nurturing microenvironment
* Development of a “runaway” immune system
* Microbiome changes that produce carcinogens or activate inflammation
* Pre-existing immune system dysfunction
* Germ line variations of inflammatory mediators



Gastric MALT lymphoma: An example of antigen driven lympho-proliferation (arrows at lympho-epithelial lesion).

Network based theory of carcinogenesis

* Our biologic networks are delicately balanced at a critical state between stimulating and dampening forces. This provides flexibility to coordinate sophisticated activities such as mitosis and apoptosis, responses to environmental and physiologic threats and to maximize our ability to evolve.
* Networks change autonomously, causing the organism to move through embryogenesis, fetal and childhood growth and development, sexual maturity and adulthood.
* These transitions are influenced by control mechanisms that keep the organism on path and are capable of responding to common threats to the health and reproductive capacity of the organism.
* Chronic stressors, including chronic inflammation, disturb this balance and create network instability, which affects cells at risk for malignancy, their microenvironment and the immune system.
* Over time, the instabilities are amplified and ultimately may produce network trajectories associated with intermediate states which may (hyperplasia, dysplasia, gastric atrophy) or may not be identifiable histologically (glioblastoma).
* Intermediate states interact with each other and with chronic stressors to produce cancer attractor states (Huang 2009), which may represent reactivation of embryonic or inflammatory states.
* These cancer attractor states are difficult to reverse.

References

* See NatPernick.com for full paper and supporting references
* Huang. Cancer attractors. Semin Cell Dev Biol. 2009 Sep;20(7):869-76.

Treatment

* Curative treatment must focus on cellular networks which create malignant properties, cause additional cancers due to field effects and are important in understanding and overcoming treatment resistance.
* There can be no “silver bullets” for cancer and talk of a “world without cancer” is irrational.
* Treating varied aspects of the disordered networks is required to attain high cure rates for disseminated and advanced disease.

1. Treat life threatening aspects of disease.
(a) Kill or limit primary tumors;
(b) Use more diverse treatment combinations than for childhood malignancies because adult tumors are caused by chronic stressors, are heterogeneous and are multifocal;
(c) Removal of the primary may not cause reversion of altered networks throughout the body to normal.

2. Move networks towards more stable attractors or less hazardous states.
(a) Destabilize these networks if necessary;
(b) Promote maturation and differentiation pathways;
(c) Stimulate pathways which halt processes associated with malignancy (embryonic rapid cell division, chronic inflammation, wound healing, liver regeneration) or otherwise “steady” networks.

3. Reduce behavioral chronic stressors (risk factors).

4. Counter non-behavioral chronic stressors to the extent possible.

5. Target microenvironmental factors that nurture tumor cells.

6. Identify and counter impaired immune system function.

7. Identify and target germ line changes associated with tumor production.

8. Develop more effective screening of premalignant lesions.

9. Optimize rational medical care.