How Lung Cancer Arises, Based on Complexity Theory

Nat Pernick, M.D.

Bingham Farms, Michigan (USA)

NatPernick@gmail.com

Background

• The War on Cancer has failed, particularly for lung cancer.
• Lung cancer causes 25% of U.S. cancer deaths, estimated at 154,050 deaths in 2018.
• Overall 5 year survival, although increasing, is only 7% for small cell and 21% for non small cell lung carcinoma.

Reductionism and Complexity

• Current cancer research is based on reductionist thinking, which is characterized as "the behavior of the whole is equal to the behavior of the sum of its parts."
• Reductionism is inadequate in biology because it cannot predict important features such as the 3D structure of proteins or the impact of genetic changes and it provides only limited understanding of basic cellular functions such as mitosis.
• For an adequate understanding of cancer, it is important to study complexity science and self-organization, summarized in Table 1. They focus on interactions between the parts, which lead to the emergence of novel properties that cannot be predicted and may even be surprising.
• We have proposed that chronic cellular stress causes most cancer by disrupting aspects of biologic networks that maintain homeostasis and ultimately pushes susceptible stem / progenitor cells into unstable network trajectories associated with relatively uncontrolled cell division.
• Initial network changes may be subtle with minimal molecular or histologic changes but ultimately large "catastrophes" of network change may arise that are identifiable as premalignant or malignant based on histology or molecular patterns.
• Table 2 lists 9 important chronic cellular stressors.

Table 1 - The Laws of Complexity and Self-Organization

1. In life, as in other complex systems, the whole is greater than the sum of the parts.
2. There is an inherent inability to predict the future of complex systems.
3. Life emerges from non-life when the diversity of a closed system of biomolecules exceeds a threshold of complexity.
4. Much of the order in organisms is due to generic network properties.
5. Numerous biological pressures push cellular pathways toward disorder.
6. Organisms resist common pressures toward disorder through multiple layers of redundant controls, many related to cell division.
7. Neoplasia arises due to failure in these controls, with histologic and molecular characteristics related to the cell of origin, the nature of the biologic pressures and the individual's germ line configuration.

Table 2 – Chronic Cellular Stressors That Cause Malignancy

1. Chronic inflammation (due to infection, infestation, autoimmune disorders, trauma, obesity, diabetes and other causes)
2. Exposure to carcinogens
3. Reproductive hormones (estrogens, androgens)
4. Western diet (high fat, low fiber, low vegetable consumption)
5. Aging
6. Radiation
7. Immune system dysfunction
8. Germ line changes
9. Random chronic stress / bad luck

Population Attributable Fraction

The population attributable fraction (PAF) is the projected reduction in death or disease that would occur if exposure to a risk factor were reduced to an alternative ideal exposure scenario, such as no exposure. Since lung cancer has multiple risk factors with synergistic interactions, PAFs often overlap and add up to more than 100%. The literature is summarized in Table 3.

Table 3 – Population Attributable Fraction of Lung Cancer Risk Factors

Risk Factor	All	Never smokers
Tobacco (smoking)	80%	N.A.
Secondhand smoke	5%	North America M: 8.2%, F: 5.6%
Random chronic stress	N.A.	50-70%
Radon	10%	M: 19-26%, F: 20-27%
Occupational	10%	N.A.
Outdoor air pollution	1-2%	N.A.
Tuberculosis	N.A.	North America 1.1%, Europe 2.4%
Germ line variations	N.A.	North America 2.0%, Europe 1.2%
COPD	N.A.	North America 0.4%, China 0.6%
Pneumonia	N.A.	North America 0.2%
Indoor air pollution	N.A.	China 19.9% (coal use, women)

Unspecified attributable risk: aging, diet, HIV, HPV, obesity

N.A.: not applicable or data not available
M: male, F: female
COPD: chronic obstructive pulmonary disease

Treatment Approaches to Lung Cancer Based on Complexity Theory

1. Successful treatment must address tumor heterogeneity.
(a) Curative treatment for lung cancer may require more treatment diversity than curative treatment for childhood leukemia, Hodgkin lymphoma or testicular cancer, which typically affect the young, have no prominent risk factors and show no field effects. In contrast, lung cancer has a median age of 70 years and has major risk factors with well established field effects:
* Tobacco smoke causes 80% of lung cancer and has heterogeneous effects due to 60+ carcinogens and decades of exposure, which likely activate different pathways at multiple sites within the lung.
* Other risk factors also produce tumor heterogeneity.
* Thus, treatment based on a single tumor feature is unlikely to be curative.

2. Treatment should halt and optimally act to reverse the chronic stressors.
(a) For example, antibiotics cure most cases of gastric MALT lymphoma by reversing antigen dependent lymphoproliferation; anti-estrogens and anti-androgens are effective against breast and prostate cancer by reversing the proliferative effects of these hormones.
(b) These treatments affect both existing malignancies and their precursors.
(c) We do not know how to reverse network changes caused by radon or other "simple" carcinogens, much less tobacco smoke containing multiple complicated carcinogens acting independently and synergistically at numerous cell targets. Tobacco smoke also triggers chronic inflammation, which promotes carcinogenesis via other pathways.
(d) It may be helpful to minimize or counter all known chronic cellular stressors related to lung cancer and to detect and counter the inflammatory process.

3. Moving cancer networks into less lethal states may be useful.
(a) New treatments could move cancer networks into less lethal states.
(b) Attractor: a stable equilibrium state corresponding to gene expression profiles specific to each cell type.
* This low energy state "pulls in" cells with similar network configurations.
* Attractors stabilize cellular networks against common perturbations.
(c) Malignant cells may exhibit gene expression profiles called cancer attractors that pre-exist in healthy genomes but are normally not accessible, analogous to dangerous cliffs that are avoided by well planned highways.
(d) Chronic cellular stress may move cellular networks from physiologic attractor states to intermediate malignant states and ultimately to cancer attractors.
(e) Drugs which destabilize existing states may move them towards a more differentiated or less hazardous state, including:
* Maturational agents such as retinoids for acute promyelocytic leukemia or progestin for endometrial intraepithelial neoplasia
* Factors halting wound healing or liver regeneration
* Factors halting rapid cell division in embryogenesis

4. Targeting chaos may be useful.
(a) Lung cancers often exhibit chaotic properties or other instability and may express biomarkers from lung developmental networks.
(b) New therapies such as immune checkpoint inhibitors may target the large mutational burden of aggressive tumors or other aspects of their chaotic or unstable states such as cell-extracellular matrix detachment.

Additional Findings

1. Lung cancer in never smokers may be a distinct disease from lung cancer in smokers.
• Lung cancer in never smokers causes an estimated 300,000 annual deaths and is the ninth most common cause of cancer death.
• Compared to smokers, never smokers with non small cell lung cancer have these characteristics:
* Women (62% vs. 36%)
* Asian, Pacific Islander, Hispanic (15% vs. 4%)
* Adenocarcinoma subtype (61% vs. 36%)
* *EGFR* mutations (36% vs. 8%)
* *ALK* rearrangements (26% vs. 4%)
* Superior survival (507 vs. 330 days), possibly because tobacco smoke creates tumors that are more multifocal, aggressive and unstable, features traditionally associated with poorer survival.

2. Random chronic stress / bad luck causes an estimated 50-70% of lung cancer in never smokers and a baseline incidence of lung cancer worldwide of 2 cases per 100,000.
• To assess this "risk factor", one must rule out known risk factors that may not be obvious (radon, secondhand smoke, Western diet) or have a small overall impact (COPD, pneumonia, infections, germ line variations, obesity).
• Since there are no known chronic stressors to halt for this "risk factor", it may be prudent in designing treatment to try to detect and counter any existing inflammatory process.

Selected References

• See NatPernick.com for links to articles supporting Tables 1 and 2.

• Cancer Facts and Figures 2018 (American Cancer Society).

• The Health Consequences of Smoking - 50 Years of Progress: A Report of the Surgeon General 2014.

• Other references available upon request.