The importance of systemic networks in cancer treatment

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Cancer is a systemic disease. This means it is important to treat not just the obvious tumor mass but also the systemic cellular networks that nurture the tumor. Surprisingly, most cancer treatment plans ignore the systemic networks.

Targeting systemic tumor networks will be difficult, requiring combinations of combinations of therapy. We will need different therapeutic strategies for the primary tumor and many of the systemic networks. Each type of therapy may need to consist of combinations of treatments to block a sufficient number of steps in the web-like pathways that exist for each cellular function.

This subject was discussed in the abstract below, which was not accepted at a recent conference. Although disappointing, the advantage of this rejection is that I can publish it now without any copyright restrictions. The full paper is at **http://www.natpernick.com/PancreaticcancerFeb2021.html**. Please send your comments to **Nat@PathologyOutlines.com**.

Monitoring Dysfunctional Networks To Support Curative Treatment of Pancreatic Cancer

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Context: Pancreatic cancer is a systemic disease with dysfunctional networks that must be treated and monitored, in addition to the primary tumor.

Design: We calculated the population attribution fraction of pancreatic cancer risk factors and reviewed their mechanisms of action within the context of complexity theory to determine common features, principles of curative therapy and key network issues.

Results: Random chronic stress causes 25-35% of cases, non O blood group 17%, excess weight 15%, cigarette smoking 15%, type 2 diabetes 9%, alcohol 5%, diet 5%, family history / germline 2% and chronic pancreatitis 1% (Table 1). Risk factors can be categorized into 5 “super promoters”: chronic inflammation, DNA alterations, random chronic stress / bad luck, immune system dysfunction (individual or “societal”) and hormones. We identified key systemic network issues that curative therapy must address and propose monitoring their response to treatment: overall inflammatory process, immune system’s antitumor capabilities, microenvironment (vasculature, inflammation, fibroblasts, extracellular matrix) of

tumor and metastatic sites, activation of unicellular-like networks, activation of embryonic networks, insulin-IGF system and germline networks that promote malignant behavior. Pathologists must create assessments of each key network's response to treatment by determining relevant biomarkers to measure and understanding how their expression affects treatment and survival. Developing a cancer network score analogous to the TNM score may be useful.

Conclusions: Pancreatic cancer has an altered systems biology with changes in systemic, nontumor networks that typically will not revert to normal by destroying the original tumor. Curative therapy requires treatment targeting these networks and monitoring their response to treatment.

Table 1 – Pancreatic cancer risk factors

Risk factor Attributable fraction

Random chronic stress 25-35%

Non O blood group 17%

Excess weight 15%

Cigarette smoking 15%

Type 2 diabetes 9%

Alcohol use 5%

Diet 5%

Family history / germline 2%

Chronic pancreatitis 1%

Table 2 – Cancer "super promoters"

Chronic inflammation

DNA alterations

Random chronic stress / bad luck

Immune system dysfunction (individual or "societal")

Hormones

Table 3 – Key systemic network issues

Overall inflammatory process

Immune system’s antitumor capabilities

Microenvironment (vasculature, inflammation, fibroblasts, extracellular matrix) of tumor and metastatic sites

Activation of unicellular-like networks

Activation of embryonic networks

Insulin-IGF system

Germline networks that promote malignant behavior