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%. 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.