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UNCOVERING DISEASE NETWORKS USING COUNTERTERRORISM APPROACHES

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Abstract

Despite an ever-increasing amount of biomedical research data and the increasing capabilities to monitor and analyze patients' data, the underlying mechanisms of disease are still poorly understood. Network models of biological interactions offer insights into disease progression with the goal to improve diagnosis, prognosis and therapeutic interventions. Biological networks can be drawn as directed graphs whose nodes are biological entities and whose arcs are the interactions among those entities. The entities range from molecules or cells at the lower levels, moving up to tissues, organs, organism and populations. The arcs can represent structural or functional entity interactions and can be dynamic over time. Although biological network models based on Internet or social network analogies may be useful, their focus on hubs runs contrary to the distributed nature of progression in diseases such as cancer. We propose that terrorist network models may help uncover hidden disease networks by using qualitative and quantitative methods traditionally used for military, defense, and security applications, including – but not limited to – those used in counterintelligence, counterinsurgency and counterterrorism efforts. Examples will be drawn from disease networks including metastasis of renal cell carcinoma.

Keywords: systems biology, network models, disease, counterterrorism, cancer

Introduction

Despite an ever-increasing amount of biomedical research data and the increasing capabilities to monitor and analyze patients' data, the underlying mechanisms of disease and their association with clinical outcome are still poorly understood. A key question is how to assemble the vast building blocks of information about disease into a mental model or conceptual framework that can be analyzed to improve diagnosis, prognosis and therapeutic interventions.

Here we present a novel conceptual framework of disease progression as analogous to terrorist activity, with suggested applications in cancer research. Despite more than 40 years of National Cancer Institute sponsored research [3], cancer accounts for nearly one of every four deaths in the United States [4]. By framing disease activities within well-researched models of terrorism, qualitative and quantitative methods traditionally used for military, defense, and security applications may be utilized for improving diagnosis, prognosis and therapeutic interventions.

Background

The intelligence community has long been aware of its similarities to the medical profession. Both professions collect, analyze, and disseminate data, and require judgment to resolve ambiguities [5]. Both labor under uncertainty and the unpredictable behavior of their actors and activities; both track identifiable problems that change over time [6]. Both need the insight of "generalists" (such as attending physicians) with a broad scope of competencies to integrate specialist knowledge and prescribe a course of action [7, 8].

After the terrorist attacks on the United States in September 2001, theoretical and applied research into counter-terrorism escalated, with publications ranging from the cognitive informatics of intelligence analysis [9] to building the perfect terrorist cell [10]. In particular, much work has been done in modeling terrorist organizations as networks in order to uncover potential strengths and weaknesses [11]. It has been known for some time that covert networks are structured differently from common networks such as social networks, the internet or electric power grids; illegal networks evolve to maximize concealment and cascade resilience rather than operational efficiency [12, 13].

Both professions share similar semantics and semiotics. They both deal with cells and fight disease. The similarities are strongest in chronic diseases [6], and strikingly so in cancer. This suggests that analytical tools used for counter-terrorism may assist cancer research.

Conceptual Model

The purpose of a conceptual model of cancer metastasis is to generate novel research questions based on similarities between the activities, actors, structures and goals of cancer and terrorist organizations, so that counter-terrorism analytical methods may be used. In the conceptual framework of Figure 1, the actors are cancer and terrorists. Their destructive activities are supported by signaling and supply lines: visible, hidden, or transformed.

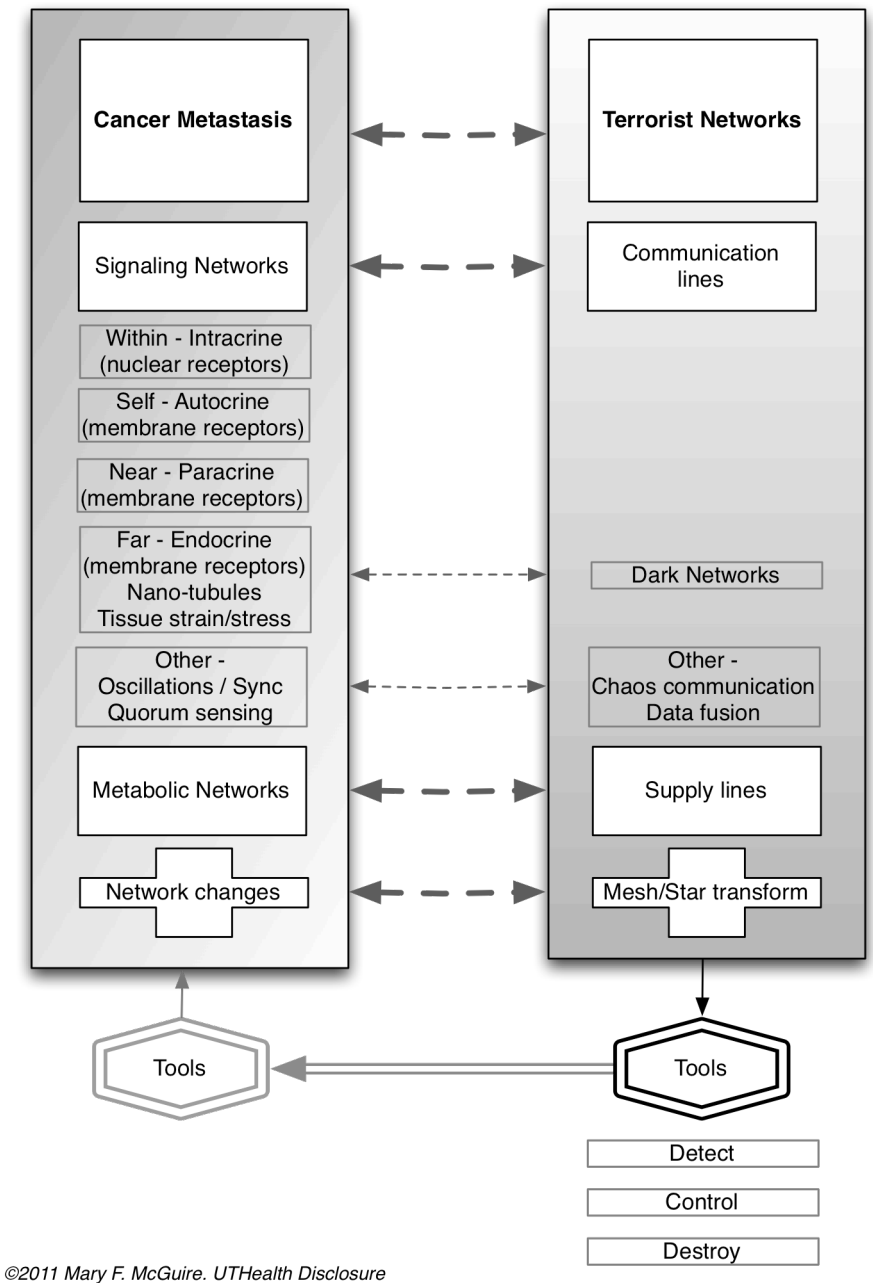

Figure 1. Conceptual Framework: Cancer and Terrorism

Following are some examples of parallels in cancer and terrorism:

- "Hiding in Plain Sight". Deception and denial have long been a part of military operations. Just as the terrorist Osama bin Laden was found in 2011 in a middle-class neighborhood near a military academy in Abbottobad, Pakistan [14], tumor cells hide by co-opting and conscripting their normal neighbors [15].

- Terrorist and underground networks appear to be optimized for redundancy, evasion, and cascade resilience using a connected star structure [13]. If metastasis networks (Figure 2) can be modeled as star networks, counter-terrorism network analytics may prove useful. Note that the constellation Cancer is a star network of stars (Figure 3).

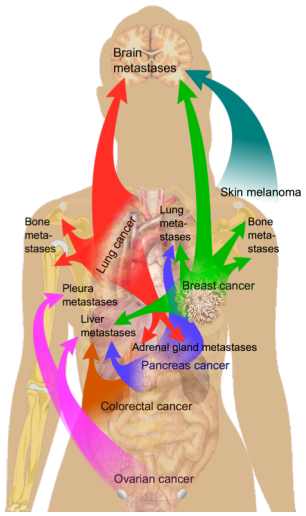

Figure 2. Metastasis sites in Cancer [1]

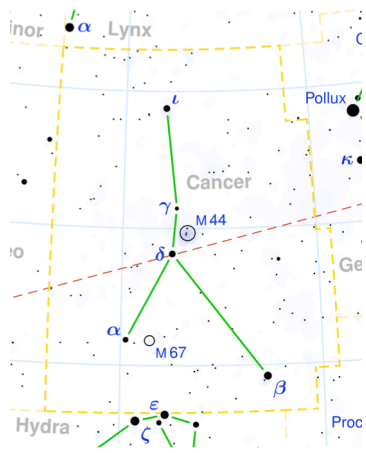

Figure 3. Cancer constellation map [2]

Research Questions

From the network perspective, it is known that cancer "hijacks" and transforms normal biological pathway networks of signaling and metabolism [16]. The conceptual framework of cancer as terrorism suggests a number of research questions.

- Does cancer change normal networks into connected stars? Consider normal networks graphically as interconnected meshes. In the mathematics of electronic networks, one can transform a mesh network to an equivalent star network (also called a delta-wye transform) when specific conditions are met [17]. Is this what is happening in cancer?
- Do different cancers form networks of different shapes? Are there typical characteristics common to all cancer networks?
- Does cancer utilize "dark" networks for its activities? "Dark" networks are networks hidden from view, largely inaccessible, and resistant to data collection [18]. In the same way that a human has a coccyx –a vestigial tail, there are likely vestigial networks. This has been shown in other species, and has been suggested as an approach to finding human drug targets [19]. The "canonical" pathway networks associated with cancer signaling and metabolism are primarily biochemical and difficult to study beyond the molecular, cellular and tissue levels. Recently other types of multi-level (from molecule to organism level) networks have been uncovered in the body. There are intercellular nanotubes that transfer components between cells and transmit pathogens such as human immunodeficiency virus (HIV)-1 over long distances [20] as well as support electrical synchronization between distant cells [21].

Finally, biochemical networks collaborate with "stress and strain" networks to facilitate the migration of tumor cells [22].

- How does cancer modify networks? It is hypothesized that tumors become irrevocably addicted to the continued expression of the proteins from genes that started the tumor – a process called oncogene addiction [23] which is the basis for many targeted cancer therapies [24]. Another recent suggestion has been that of oncogene amnesia, wherein cancer makes cells forget their checkpoint mechanisms [25]. In the former hypothesis, network arcs are broadened; in the latter, they are cut.

Application of Conceptual Model

This conceptual model of cancer is currently being applied to a study of epithelial-mesenchymal transition in recurrent metastatic renal cell carcinoma, and preliminary results will be presented at the workshop.

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