

TOWARDS TRANSLATIONAL SYSTEMS BIOLOGY AND PERSONALIZED MEDICINE IN CANCER

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[1] INTRODUCTION

Living cells are characterized by their ability to perceive and correctly respond to their microenvironment. This process is called cell signaling and it governs basic cellular activities and coordinates cell actions [1]. Signal transduction processes form the basis of cell growth, tissue repair, and immunity as well as normal tissue homeostasis. Distorted cell signals lead to diseases such as cancer, autoimmunity, and diabetes. By understanding cell signaling, can result in effective diagnostic and therapeutic solutions to treat diseases.

Cancer continues to cause a major public health crisis. According to the World Health Organization, cancer accounted for 7.6 million deaths (around 13% of all deaths) in 2008. Irrespective of the environmental factors involved in causing cancer, cell signaling is involved at some level. Cancer cell have a proliferative advantage because they deregulate, up-regulate or inhibit pathways and signaling is by default mechanistically involved in cell development.

Cancers are extremely robust [2], complex, heterogeneous diseases due to dynamic network behavior and signaling pathway crosstalk within the cell. The significance of genetic mutations in cancer development is emphasized by Hanahan & Weinberg where they refer to six critical changes in cell functioning that describes malignant cancer growth as the hallmarks of cancer. The following six changes incorporate some aspect of genetic mutation and evolutionary selection causing malignant progression: (a) self-sufficiency in growth signals; (b) insensitivity to anti-growth signals; (c) evading apoptosis; (d) limitless replicative potential; (e) sustained angiogenesis; and; (f) tissue invasion and metastasis [3]

Cancer is now not only a highly heterogeneous pathological condition but a multiscale problem [4]. The intimate connections between genes, signaling networks, subcellular organelles, and phenotypic traits are perturbed in a typical cancer cell. Cancer is defined by an extraordinary amount of heterogeneity among genes involved in tumorigenesis. If such a signaling network involving hundreds of proteins is disturbed or altered, a cancer phenotype could be generated. The

genotypic and phenotypic variation makes understanding the processes driving tumorigenesis extremely challenging. To understand how signaling networks disrupt cellular behaviors causing cancer, it is necessary to use a systems approach.

Systems biology is an interdisciplinary field deriving concepts from the life sciences, engineering disciplines and computer science. This new field accentuates the functionality of all components working together and augments the traditional way of studying the individual roles of single components. Systems biology represents a quantitative approach to biology; thus demands collaborations between quantitative & non-quantitative disciplines and multidisciplinary teams [5].

High throughput technologies have led to detailed characterization of biochemical networks by allowing us to measure cellular components with few experiments. The challenge is to understand how cellular components are organized into a complex network based on the measurement of individual components, to understand causes of diseases and find effective drugs. The reconstruction and analysis of complex biological networks, such as metabolic networks, gene regulatory networks and protein-protein networks (PPN) are central topics of Systems Biology [6].

Incorporating and consideration for the multifunctionality of network components is important to fully comprehend biochemical pathways. Further, stoichiometric network reconstruction and associated mathematical analyses can be included to study genome-scale networks properties. Combining these analyses with experimental studies, new hypotheses can be generated about the interplay among the biochemical networks [7]

Systems biology is a unique integrative approach involving theoretical modeling and direct experimentation. Experiments provide data for model design and theoretical models provide insights into experimental observations, while the experiments confirm or refute model findings. Thus, multidisciplinary approach is ideal to understand systems biology. Researchers

from molecular biology, engineering, physics, computational science, statistics, chemistry, and mathematics need to cooperate in order to explain how the biological system work cooperatively and coherently [8].

Similar to interconnected roads in our cities, biomolecules inside cells are also networked. This suggests that biochemical pathways have cross-talk, which allows cancer to bypass the effects of a drug. Therefore, cancer needs to be treated with alternative molecular routes and target multiple genes. A systems perspective, rather than the current gene-centric view, could solve these issues and facilitate new options for cancer treatment and identify the most promising potential new drugs [9].

The systems biology approach integrates empirical, mathematical and bioinformatics techniques to understand the intricate biological and physiological processes. Systems biology helps by generating detailed blueprints depicting different kinds of cellular networks and by developing sophisticated mathematical, statistical and computational methods and tools to analyze these networks.

Understanding cancer requires development of mathematical models capable of generating testable predications and powerful hypotheses. In order to better understand cancer, a model must describe or accommodate the Weinberg's hallmarks of cancer. While focusing on these common aspects, mathematical modeling aims to contribute to the prevention, diagnosis and treatment of this complex disease.

CONFLICT OF INTEREST

The author declares no conflicts of interest.

REFERENCES

- [1] Witzany G. (2000) Life, the communicative structure : *a new philosophy of biology*. Norderstedt: G. Witzany.
- [2] Kitano H. (2004) Cancer as a robust system: implications for anticancer therapy. *Nat Rev Cancer* 4(3): 227–235.
- [3] Hanahan D and Weinberg RA. (2000) The hallmarks of cancer. *Cell*, 100(1): 57–70.
- [4] Rothschild Anderson AR and Quaranta V. (2008) Integrative mathematical oncology. *Nat Rev Cancer*, 8(3): 227–234.
- [5] Tadmor B, and Tidor B. (2005) Interdisciplinary research and education at the biology-engineering-computer science interface: a perspective (reprinted article). *Drug Discovery Today* 10(23-24): 1706–1712.
- [6] Ma HW, and Goryanin I. (2008) Human metabolic network reconstruction and its impact on drug discovery and development. *Drug Discovery Today* 13(9–10): 402–408.
- [7] Gianchandani EP, Brautigam DL, and Papin JA. (2006) Systems analyses characterize integrated functions of biochemical networks. *Trends Biochem Sci* 31(5): 284–291.
- [8] Hood L. (2003) Leroy Hood expounds the principles, practice and future of systems biology. *Drug Discov Today*, 8(10): 436–438.
- [9] Wang E. (2010) Cancer Systems Biology (Vol. in press): Chapman & Hall/CRC Press.