Translational Medicine
ISSN: 2161-1025

Chiriva-Internati et al., Transl Med 2013, 3:1
DOI: 10.4172/2161-1025.1000e116

Editorial Open Access

Translational Medicine, Biomarker Discovery and Tumor Complexity

Maurizio Chiriva-Internati[1]*, Everardo Cobos[1], Jose A Figueroa[1] and Fabio Grizzi[2]

[1]*Department of Internal Medicine at the Division of Hematology and Oncology, The Southwest Cancer Treatment and Research Center, Texas Tech University Health Sciences Center, Lubbock, TX, USA*
[2]*Laboratory of Molecular Gastroenterology, Humanitas Clinical and Research Center, Rozzano, Milan, Italy*

Despite years of intensive investigation, resulting in a better understanding of its etiology and major advances in treatment, cancer remains a major cause of death worldwide. Human cancer emerges from multiple and complex alterations in the expression pattern of genes, ultimately leading to dysfunctional protein networks and deregulation of critical cellular events. One of the primary tasks of cancer research is the discovery and translation of molecular cancer *biomarker* candidates into clinical practice. Unfortunately, there is no agreement with regard to the sequence and nature of steps necessary to warrant an efficient translation of these prognostic and/or predictive biomarkers into clinical use and how to utilize them for the implementation of novel, less toxic and more effective therapeutic strategies against this disease [1].

Cancer is a highly heterogeneous disease, with more than 100 distinct types of human neoplasms described and various tumor subtypes found within specific organs. This genetic and phenotypical variability is what primarily determines the *self-progression* of neoplastic disease and its response to therapy [2,3]. Individual cells from a clonal cell population respond differently to the same stimulus and this variability is the basis for both inherent and acquired resistance to therapeutic interventions [4,5]. In this context, each cancer therapy can be viewed as a "filter" that removes a subpopulation of cancer cells that are sensitive to a given treatment, while allowing insensitive subpopulations to escape [6].

In heterogeneous populations, patients display a multiplicity of genetic variations that respond differently to a given medical intervention, resulting in the observation that identical treatments could benefit some patients yet be harmful to others [7,8]. Moreover, the complexity of tumor-host interactions, caused by temporal changes in tumor phenotype, and the array of immune mediators expressed within the tumor microenvironment, plays a major role in cancer behavior and may partially explain the limited reliability and applicability of current therapeutic approaches, including those designed to manipulate the host's immune system [9,10].

Human carcinogenesis is a dynamic process that depends on a large number of variables regulated at multiple spatial and temporal scales not clearly following predictable and repeatable pathways [2,3]. This multiple scale causality not only recognizes processes and controls acting at multiple scales but, unlike a strictly reductionist approach, also supports the notion that relevant "first principles" may reside at scales other than the smallest molecular and cellular micro-scales. In other words, the observed phenomenon at each scale has structural and behavioral properties that do not exist at lower or higher organizational levels. As an example, a number of Tumor-Associated Antigens (TAA) have been recognized and proposed as potentially useful targets when designing immunological treatments for cancer. However, the expression of TAA in biological materials has mainly been studied at the level of gene expression using Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) analysis and the Quantitative real-time PCR (qrt-PCR) technology [11], and the information provided by these approaches has been limited by the fact that the phenomena observed at each level of anatomical organization (*i.e.* gene, cell, tissue, organ, system or apparatus and the organism as a Whole) have properties that do not exist at a lower or higher organizational levels. Therefore, RT-PCR and qrt-PCR may offer a satisfactory qualitative/quantitative description of small-scale structures, but may be irrelevant to large-scale features [11].

In mathematical terms, carcinogenesis is a non-linear process [2,3]. These non-linear systems are characterized by three basic properties: *(a)* they do not react proportionally to the magnitude of their inputs; *(b)* they depend on their initial conditions and *(c)* their behavior is not deterministic, *i.e.* periods of inactivity may be punctuated by sudden change, apparent patterns of behavior may disappear and new patterns surprisingly emerge. Such behavior emerges in complex systems, and is permanently sensitive to small perturbations. In order to understand human cancer as a complex system, we need to determine the type of data that needs to be collected at each level of organization, the boundary conditions to use when describing the disease (*i.e.* a perturbed system), and the technologies and approaches best suited to reveal its underlying biological behavior [2,3]. Critical analysis of traditional approaches employed to understanding cancer evolution and designing therapeutic interventions are needed that take into account tumor complexity. Therefore, it becomes necessary to incorporate the concepts of multiple scale causality and heterogeneity when generating new medical interventions.

Since our understanding of human cancer is still limited, and pre-clinical models have shown a discouraging propensity to fail when applied to humans, a new way of thinking is desperately needed that unites physicians, biologists, mathematicians and epidemiologists, in order to develop a better theoretical framework of tumor development, progression and tumor-host interactions [12,13-18]. The use of a holistic approach, enabling a more accurate selection of immunotherapeutic target antigens in the first phase of the experimental research, will reduce the notable fragmentation of the biological information in the post-genomic era, and will facilitate a more accurate transfer of this acquired pre-clinical knowledge to the bedside. This new way of thinking may help discover biomarkers with potential clinical value.

References

1. Hörig H, Marincola E, Marincola FM (2005) Obstacles and opportunities in translational research. Nat Med 11: 705-708.

2. Grizzi F, Chiriva-Internati M (2006) Cancer: looking for simplicity and finding complexity. Cancer Cell Int 6: 4.

***Corresponding author:** Maurizio Chiriva-Internati, Department of Internal Medicine, Division of Hematology and Oncology, School of Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas, USA, E-mail: maurizio.chiriva@ttuhsc.edu

Received January 09, 2013; **Accepted** January 11, 2013; **Published** January 13, 2013

Citation: Chiriva-Internati M, Cobos E, Figueroa JA, Grizzi F (2013) Translational Medicine, Biomarker Discovery and Tumor Complexity. Transl Med 3: e116. doi:10.4172/2161-1025.1000e116

3. Chiriva-Internati M, Grizzi F, Di Ieva A, Russo C, Frezza EE, et al.(2006) Cancer initiation and progression: an unsimplifiable complexity. Theor Biol Med Model 17: 37.
4. Bastiaens P (2009) Systems biology: When it is time to die. Nature 459: 334-335.
5. Spencer SL, Gaudet S, Albeck JG, Burke JM, Sorger PK (2009) Non-genetic origins of cell-to-cell variability in TRAIL-induced apoptosis. Nature 459: 428-432.
6. Mittra I (2007) The disconnection between tumor response and survival. Nat Clin Pract Oncol 4: 203.
7. Heng HH (2008) The conflict between complex systems and reductionism. JAMA 300: 1580-1581.
8. Luo J, Solimini NL, Elledge SJ (2009) Principles of cancer therapy: oncogene and non-oncogene addiction. Cell 136: 823-837.
9. Mantovani A, Allavena P, Sica A, Balkwill F (2008) Cancer-related inflammation. Nature 454: 436-444.
10. Anderson AR, Weaver AM, Cummings PT, Quaranta V (2006) Tumor morphology and phenotypic evolution driven by selective pressure from the microenvironment. Cell 127: 905-915.
11. Chiriva-Internati M, Grizzi F, Bright RK, Martin Kast W (2004) Cancer immunotherapy: avoiding the road to perdition. J Transl Med 2: 26.
12. Anderson AR, Quaranta V (2008) Integrative mathematical oncology. Nat Rev Cancer 8: 227-34.
13. Sogn JA, Anton-Culver H, Singer DS (2005) Meeting report: NCI think tanks in cancer biology. Cancer Res 65: 9117-9120.
14. Chiriva-Internati M, Pandey A, Saba R, Kim M, Saadeh C, et al. (2012) Cancer testis antigens: a novel target in lung cancer. Int Rev Immunol. 31: 321-343.
15. Pandey A, Kurup A, Shrivastava A, Radhi S, Nguyen DD, et al. (2012) Cancer testes antigens in breast cancer: biological role, regulation, and therapeutic applicability. Int Rev Immunol 31: 302-320.
16. Chiriva-Internati M, Mirandola L, Yu Y, Jenkins MR, Gornati R, et al. (2011) Cancer testis antigen, ropporin, is a potential target for multiple myeloma immunotherapy. J Immunother. 34: 490-499.
17. Chiriva-Internati M (2011) Sperm protein 17: clinical relevance of a cancer/testis antigen, from contraception to cancer immunotherapy, and beyond. Int Rev Immunol 30: 138-149.
18. Cannon MJ, Goyne H, Stone PJ, Chiriva-Internati M (2011) Dendritic cell vaccination against ovarian cancer--tipping the Treg/TH17 balance to therapeutic advantage?. Expert Opin Biol Ther. 4: 441-445.