

Editorial

Systems oncology: A new paradigm in cancer research

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Since the time the word oncology was coined in 1857, the field has expanded exponentially metamorphosing the original connotation and intent of the word (Roman word “oncos” (swelling) in relation to the tumors). The word oncology should, then, literally mean the study of swelling or tumors. In a premolecular or pregenomic era, oncology was confined to diagnosing and treating the solid tumors, which was later expanded to include hematological malignancies, which are now referred to as liquid tumors. The word liquid tumor is a misnomer, in that context, but it is a topic for another discussion on another day. The advent of DNA era has focused on seeking answers to the origin of tumors in the genetics under the genetics paradigm or genetics-only paradigm. The rapidly evolved disciplines of molecular biology, biotechnology and related disciplines have enormously contributed to the understanding of tumors and tumorigenesis. The genetic paradigm has recently been sharing its prime spot with the epigenetic phenomenon that could explain the tumorigenesis and has a promise for reversibility of the process. The most recent and exciting paradigm of tumorigenic process relates to cancer stem cells. Therefore, the concepts and models of tumorigenesis are still evolving and the field seems to be far from fully explored.

THE JOURNEY OF ONCOLOGY AS A FIELD, FROM A FIELD TO STUDY TUMORS OF UNKNOWN ETIOLOGY AND CHARACTERISTICS, HAS BEEN VERY EVENTFUL FOR THE HUMAN RACE, BUT SEEMS TO BE HIJACKED BY THE COMPULSIONS OF **ONCONOMICS**, A TERM I SUGGEST TO PARTLY DESCRIBE THE ECONOMICS OF ONCOLOGY DRUG DISCOVERY AND DEVELOPMENT AND THE PAYER DYNAMICS.

So, I ponder, if cancer is a disease or a phenomenon? I tend to believe that cancer is a phenomenon. The conceptual frameworks used so far to understand cancer, from its origin to the development of therapeutics to treat, are based on the deep-rooted notion that cancer is a single disease

with diverse molecular manifestations in different organ sites. This notion seems to be strongly subscribed to and is used for diagnostics and therapeutic development as it offers an opportunity for clinical intervention. Interestingly, a general framework for oncology drug discovery is based on the ability to target an up-regulated molecule, in many cases a protein. A critical gap in this approach is the missing knowledge about the cause of events leading to up-regulation.

Expression of a protein resulting from a gene fusion, like BCR-ABL, is easy to address by inhibitors, but they represent a rare genetic phenomenon leading to cancers. Even in those cases where the drugs prove effective, how sure are we that the underlying causes of molecular dysregulation are re-balanced by the therapy?

The Journey of Oncology as a field, from a field to study tumors of unknown etiology and characteristics, has been very eventful for the human race, but seems to be hijacked by the compulsions of **onconomics**, a term I suggest to partly describe the economics of oncology drug discovery and development and the payer dynamics. The major casualty of onconomic considerations seems to be the incentive to address cancer as a phenomenon rather than as a disease in need of desperate treatment. The governmental attitude, around the world, to the need for robust, long term and

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sustainable basic research has in fact resulted in diminished interest to seriously look for the cause of the malady.

Carcinogenesis as a process is not expected to start overnight, not even in a few weeks. It has been estimated that it would take decades for cancer to manifest after exposure to carcinogens. This duration between the exposure and the manifestation of cancer, assuming direct correlation, seems to be shortening as can be seen by the lower age of onset of somatic cancers. Population and demographic differences in the incidence of cancers and the outcomes of treatment suggest a gap in our core understanding of the carcinogenesis process. The noncanonical and nonstochastic events and outcomes in the carcinogenic pathway alert us to the need to look at cancer as an end point of a series of nonlinear, systemic imbalances rather than as a result of an isolated molecular assault. In a simplistic view, a tumor is an accumulation of camaraderie of dysregulated, dysfunctional or mis-functional cells resulting from the colonization of a single renegade cell. How does one look at the trajectory of this renegade cell?

From the time a cell has been subjected to molecular insult to the stage it becomes fully committed nonconformistic member of the normal colony, the cell is a part of a series of voluntary and involuntary events. In a well-developed species such as *Homo sapiens*, all carcinogenic exposures, both exogenous and endogenous, do not result in mutagenesis; all mutagens do not produce cancer-prone cellular lineage. What happens between the deleterious encounter with harmful exogenous agents and the manifestation or lack thereof, of the ill-effects of the assaulting agent? Humans are not simple machines that treat the incoming materials and messages as static inputs. Human systems are biologically evolved to intelligently metabolize or purge through the secretory system. Innate and adaptive immune systems are at the core of protecting human cellular integrity. Often, the power of human immune machinery is overlooked, while discussing the carcinogenic potential of agents originating in the environment and diet. Cellular memory following microbial and viral infections is another concept that needs to be integrated into the framework of understanding carcinogenesis and in the drug discovery process. The tools and technology to decipher the molecular and cellular footprints involved in the carcinogenic process are yet to

be fully developed and perfected. In my opinion, this gap is mostly due to lack of comprehensive phenomenological framework to understand cancer and carcinogenic processes.

Where is the field of oncology going? Does the long pipeline of potential drugs and the list of drugs in use that extend the life a few months indicate the accomplishments of oncology as a field? The pipeline of drugs in the industry should not be misread as a measure of success against cancer or as an indication of mastery of **carcinome**, a term I propose to describe a complex system that runs the kingdom of renegade cells. Nor should we expect that the molecular profiling of a “whole genome” or a “whole proteome” results in clear messages about the culprits and the Samaritans.

I have provided arguments to drive the point that cancer and the carcinogenesis processes are complex and efforts to delineate them need to be more sophisticated than are currently employed. Looking at cancer from a systems oncology perspective will enable us to investigate the

pathways from normal to tumor cells, behavior of pretumor and tumor cells, interactions and adaptability of normal and tumor cells, and in fact, the differences in survival motives of normal and tumor cells.

It may be tempting to draw comparisons between the proposed systems oncology and the systems biology. At the outset,

the major difference is that systems oncology, enunciated in this editorial, encompasses the study of a disease or a phenomenon, from the perspectives of the multitude of disciplines such as immunology, cell biology, and molecular biology and so on. It proposes to investigate cancer in an integrated fashion utilizing the tools and methods of individual disciplines. Systems oncology opens a new way to look at treatment of cancers, therapeutic development, and understanding of the genesis of cancers at a deeper level. Journal of Carcinogenesis has already moved in this direction by introducing therapeutics as a part of its scope and is geared to be at the forefront of this new field by publishing excellent articles that represent the spirit of Systems Oncology.

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