Computational and Systems Biology of Cancer

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Ever since the war on cancer was declared in 1971, there has been an explosion in our understanding of this diverse group of diseases. The application of molecular genetics and molecular biology technologies have enabled a deep understanding of the genetic, epigenetic, signaling cascades, survival pathways, and invasive mechanisms that underlie the cancer phenotype [1,2]. Concomitantly this has translated in the development of ever more effective and safe medications that work through different mechanisms of action and target fundamental aspects of the biology of the tumor. The paradigm has been chronic myeloid leukemia where the discovery of the Philadelphia chromosome [3], ultimately led to the identification of the *BCR-ABL* oncogene and the development of tyrosine kinase inhibitors such as imatinib, nilotinib, dasatinib and others and lead to rapid, deep and long-lasting remissions in this disease [4-6]. Another success story has been acute promyelocytic leukemia with the vast majority of patients now being cured of the disease without the need for any classical chemotherapy [7].

The rapid development of deep sequencing technologies has enabled the discovery of multiple mutations and a deeper understanding of the complex 'structure' of the tumor as being composed of multiple subclones that are competing with each other for resources [8-15]. The subclones are being selected for or against by therapy [16]. Principles from evolutionary biology have been applied to understand the dynamics of how these clones change in time [16,17]. It appears that in the absence of therapy neutral evolution is very important for the development of the tumor [18], but in the presence of therapy, the potential fitness advantage of resistant clones dominates. The identification of a specific tumor sequences also enables monitoring of patients using simple blood tests (liquid biopsy) [19] for the presence of disease and its burden and perhaps will be used in the future to screen people for premalignant or early malignant processes.

Naturally over the years, a major focus has been on the tumor cells themselves leading to major advances in understanding of signaling pathways that are critical for tumor cell replication, growth, survival and cell cycle regulation. This lead to the discovery of important pathways such as the JAK/STAT, PI3 kinase, AKT, and receptor tyrosine kinases (RTK) [1,2]. All of this knowledge has been translated into effective therapies for a wide variety of tumors including myeloproliferative neoplasms, hepatocellular carcinoma, renal cell carcinoma, non-small cell lung cancer, and others. The discovery of potent anti-apoptotic mechanisms that are overexpressed in tumor cells has led to the development of effective therapies targeting for the time being BCL2 but other molecules targeting MCL-1 and others are being studied.

The 'omics' revolution enabled the interrogation of the genome, epigenome, metabolome and proteome of the tumor. A new level of understanding that was perhaps quite unexpected relates to the importance of metabolism in the tumor. Alterations in glycolysis as well as the tricarboxylic acid cycle with mutations in isocitrate dehydrogenase (IDH) 1and 2 have been identified initially in brain tumors [20] and subsequently in myeloid neoplasms [21] providing a rational target for development of drugs such as IDH1 and IDH2 inhibitors have translated into improved outcomes for patients. The abnormal dependence of the tumor cells on glycolysis (Warburg effect) serves as the basis for ^{18}F-fluorodeoxyglucose based PET imaging that has provided a much better quantification of tumor burden, monitoring of the response to therapy and is often prognostic in a variety of diseases. Enhanced metabolism requires a constant supply of resources and this ties very nicely with the evidence for angiogenesis [22] within tumors, an approach that also has been translated into therapies for specific tumors especially those of the gastrointestinal tract and lung.

For many years the presence of immune cells in tumors were considered to be an epiphenomenon until in some tumors the presence of such cells was associated with improved outcome [23]. Since then the field of immune oncology has taken the cancer community by storm. Discovery of the immune checkpoint and the subsequent development of inhibitors to PD-1, PD-L1 and CTLA-4 and effective therapy of the immunologic synapse [24] has improved outcomes for many patients with cancer. The development of monoclonal antibodies targeting a wide variety of tumor antigens, as well as the generation of antibody drug conjugates also provided effective novel therapies. More recently the field took an additional boost with the development of recombinant chimeric antigen receptor T-cell therapies [25] that right now are targeting tumors that express CD19 or BCMA but major developments in the field are expected as more tumor specific antigens are studied in clinical trials and subsequently translated into practice.

These discoveries have affectively changed our review of the tumor. The tumor is composed not just of malignant cells but has a considerable supporting orchestra of mesenchymal cells, blood vessels, extracellular matrix, and immune cells all of which can help the tumor population grow. In some tumors, the malignant cell population is even in a minority (e.g. classic Hodgkin lymphoma). Viewed in this way, the cancer is an organ that has evolved in the body and can threaten the life of the individual. Development of cancer is related to the sheer number of cells present in the body, the small but inevitable mutation rate [26], the increased life expectancy of humans, environmental factors that can increase the mutation rate, and perhaps a failure of the immune system to eradicate early mutant clones [27-29]. Cancer is a problem of multicellularity and over the eons, large organisms have developed mechanisms to reduce the risk of developing cancer including specific tissue architectures that minimize the risk of accumulation and retention of mutations [30].

This holistic view of the tumor requires a systems approach for understanding and the development of curative therapies of these diseases. We live in the age of big data [31,32]. Nowadays sequencing of tumors at the time of diagnosis is becoming almost routine. The genomic diversity within tumors that arise from the same cell but in different patients is clear and requires identification of the specific driver mutations for the tumor in each individual patient and in this scenario, the average is not good enough [33]. Similarly our understanding of pharmacogenomics is rapidly increasing and hopefully in the near future, we will be able to identify the right drug or combination of drugs for the right patient with a specific tumor. This would be expected to maximize responses and minimize toxicity while providing truly personalized therapy for patients. High-resolution imaging in patients captures the tumor burden and in the future the identification of therapeutic targets using specific imaging probes will be routine [34]. Artificial intelligence aided analysis of pathological specimens will enable the further subclassification of tumors, tease out novel diagnostic markers and increase detection sensitivity [35]. Thus, the future care of the cancer patient will be much more data driven and to paraphrase Bacon, data needs to be *understood* so that it can be translated into *knowledge* that can be applied for the care of the patient (*wisdom*).

Cancer research has also transformed itself into systems science with the introduction of time dependent data and more emphasis on the physical aspects of the tumor from the perspective of physics, chemistry, engineering, and mathematics [36-39]. The development of mathematical models for cancer has a long history as has seen the application of evolution and evolutionary game theory to understand the origin and development of the tumor and resistance to therapy [40-43]. Funding of several Physical Sciences in Oncology Centers and the subsequent development of the Cancer Systems Biology Consortium (https://www.cancer.gov/about-

nci/organization/dcb/research-programs/csbc) promises to facilitate more interdisciplinary research in cancer. Given this explosion in data generation, the need for a journal specifically dedicated to the computational and systems approaches that are essential in the field of cancer is clear. For this reason our new journal 'Computational and Systems Oncology' is being launched this year. The journal has managed to attract an international editorial board that covers all the relevant fields including informatics, computational and theoretical biology, artificial intelligence, image analysis, mathematical modeling, evolutionary dynamics and game theory, immunogenetics, physical biology.

The overarching scope of this journal is to provide a platform for the dissemination of technologies and applications that facilitate the understanding of cancer from a 'systems approach'. We are also in the era of big data and cancer provides a very ripe field for the use of large data sets with many life histories to tease out which therapies may or may not work. Thus, the journal welcomes manuscripts in the fields of mathematical and computational approaches applied to tumor genomic, proteomics, metabolomics, artificial intelligence, data science, tumor immunology and immunogenetics, theranostics, molecular imaging, evolutionary dynamics and game theory.

We encourage the open sharing of computational and systems tools developed by authors for the rapid dissemination of information to enable their rapid and broad application in oncology research and practice. Thank you for considering Computational and Systems Oncology for your next publication.

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