Chinese Journal of Cancer

Conference Report

Systems biology in the frontier of cancer research: a report of the Second International Workshop of Cancer Systems Biology

Juan Cui[1], Yan-Chun Liang[2] and Ying Xu[1,2]

Abstract

The report summarizes the Second International Workshop of Cancer Systems Biology held on July 5–6, 2012 in Changchun, China. The goal of the workshop was to bring together cancer researchers with different backgrounds to share their views about cancer and their experiences in fighting against cancer, and to gain new and systems-level understanding about cancer formation, progression, diagnosis, and treatment through exchanging ideas.

The Second International Workshop of Cancer Systems Biology (ICSB) (http://ccst.jlu.edu.cn/icsb2012/), hosted by Jilin University, was held from July 5 to 6, 2012 in Changchun, China. During this two-day meeting, 21 invited speakers, 7 from China, 13 from the United States, and 1 from Canada, gave speeches covering a wide range of topics on cancer systems biology to an audience of approximately 300 people from across China. The 21 talks roughly fell into four categories: cancer genome analysis and information discovery, cancer mechanism studies, biomarker discovery, and cancer treatment strategies. By design, these talks were delivered by cancer researchers and practitioners with diverse backgrounds who may not otherwise have opportunities to meet and share their visions about cancer studies in an open and scientifically stimulating environment. Among the speakers were cancer biologists who study specific cancer pathways, computational cancer biologists who rely on large-scale *omic* data for global information discovery, computational modelers who examine dynamic properties of cancer, immunologists who study cancer in a larger context than just tumors, and clinicians who use different strategies and techniques to treat cancer patients. Having such a diverse group of people speaking to each other and to an audience with an even wider range of expertise generated much excitement. At the end of the meeting, virtually all speakers and many attendees expressed praise for the workshop as one of the best they had attended, having been impressed by the overall quality of the talks and the intellectual level of the dialog it created.

This meeting, which is the second in its series, was initiated by Professor Ying Xu (University of Georgia and Jilin University) and Professor Yan-Chun Liang (Jilin University) in early 2011. The overall consideration in organizing this annual meeting is to bring together cancer researchers with different backgrounds to share their views and experiences in fighting cancer and to gain new systems-level understanding of cancer formation, progression, diagnosis, and treatment through exchanging ideas. Professor Liang Hu, Dean of the College of Computer Science and Technology at Jilin University, generously agreed to financially sponsor the first three annual meetings of this series, which has made this and the previous meeting possible. Like in the first meeting in 2011, the organizers felt very fortunate for the opportunity to bring together this group of leaders in their respective research areas to present their science and lead discussions.

Cancer Genome/Epigenome Sequencing and Information Discovery

To understand the genetic basis of cancer, two large cancer genome sequencing projects have been initiated: one by the International Cancer Genome Consortium

Authors' Affiliations: [1]Computational Systems Biology Laboratory, Department of Biochemistry and Molecular Biology, University of Georgia, Athens, GA 30602–7229, USA; [2]College of Computer Science and Technology, Jilin University, Changchun, Jilin 130012, P. R. China.

Corresponding Author: Ying Xu, Computational Systems Biology Laboratory, Department of Biochemistry and Molecular Biology, University of Georgia, Athens, GA 30602–7229, USA. Tel: +1-706-542-9779; Fax: +1-706-542-9751; Email: xyn@bmb.uga.edu.

doi: 10.5732/cjc.012.10205

and the other by the US National Cancer Institute and National Human Genome Research Institute, named The Cancer Genome Atlas (TCGA). TCGA aims to develop a complete "atlas" of all genomic alterations involved in dozens of major cancer types. Dr. Wei Zhang (MD Anderson Cancer Center), a principal investigator of the TCGA Initiative, presented a study by his group on the implications of *BRCA1* and *BRCA2* mutations on ovarian cancer prognosis. They found that *BRCA2*-mutated ovarian cancers have higher levels of gene mutations, respond better to front-line therapy, and have a longer overall and progression-free survival. In addition, he also discussed their recent genome sequencing study of colorectal cancer, which was published in the July 2012 issue of *Nature*, as well as their bioinformatic analyses on endometrial cancer that revealed three distinct subtypes with distinct pathway- level characteristics.

Dr. Juan Cui (University of Georgia) introduced her group's recent study in which the whole genomes of five gastric adenocarcinomas and matching controls were sequenced. The density of the mutation spectrum of each cancer genome ranged from 6.8 to 13.8 mutations per Mb of DNA. In total, 407 non-synonymous somatic point variations were identified, primarily occurring in mucins and transcription factors. Seventy-six genes had copy-number changes, and 679 genomic rearrangements were detected. The study revealed that 79.6% of the chromosomal rearrangements occurred among neighboring regions in the folded chromosomes, based on mapping of the boundaries of the rearranged regions to the folded three-dimensional structures of the human chromosomes and the replication timing profiles.

In his presentation, Dr. Jin-Tang Dong (Emory University) demonstrated how a tumor suppressor gene can be identified from a chromosomal region that is frequently deleted in human cancer. Specifically, he and his colleagues presented krueppel-like factor 5 (KLF5) as a tumor suppressor gene based on *in vitro* and *in vivo* studies and reported a novel mechanism for how KLF5 can be inactivated in human cancer. Interestingly, animal studies demonstrated that KLF5 can act as both a tumor suppressor and promoter, and biochemical analyses of cultured epithelial cells revealed a possible mechanism for how KLF5 can switch functions. In their *in vitro* studies, Dr. Dong's group found that KLF5 is a cofactor of TGF-β signaling, and TGF-β-induced acetylation of KLF5 is the key event that reverses the function of KLF5. In the absence of TGF-β, KLF5 is not acetylated and promotes cell proliferation by regulating cell cycle genes. However, when TGF-β is present, KLF5 is acetylated and the acetylation reassembles the KLF5 transcriptional complex, leading to a change in gene transcription and the reversal of KLF5 function.

DNA methylation is associated with silencing or overexpression of many biologically important genes in almost all types of cancer. Dr. Dong Xu (University of Missouri) described his group's bisulfite-sequencing analysis of DNA methylation patterns across different cancer tissue samples. They identified digital profiles of aberrant DNA methylation and suggested potential methylation biomarkers for cancer subtypes. They also studied sequence and methylation patterns among DNA methyltransferases and found long-range patterns in the flanking sequences around methylation sites and cooperativity among different DNA methyltransferases. In addition, they found that DNA methylation in the 3'-UTR was positively correlated with expression of the upstream gene, in contrast to negative correlation of expression with its promoter region. Their analysis indicates that 3'-UTRs are hypomethylated in tumor samples and that genes with longer 3'-UTRs tend to have more differential methylation and thus a higher ability to regulate the gene expression.

In addition, Dr. Wen-Yi Wang (MD Anderson Cancer Center) also presented her work on cancer genome analyses and applications.

Mechanisms of Cancer

Four talks were focused on mechanisms of cancer. Speakers discussed the topic from their own unique perspectives, some with a more traditional focus on specific cancer-related pathways and others with a focus on global pictures.

Dr. Ying Xu (University of Georgia) presented a model showing that hypoxia may serve as a key driver for cancer growth. The idea of the model is that as a cell becomes increasingly more hypoxic, there is a switch in cellular respiration from oxidative phosphorylation to glycolysis, which was first reported 90 years ago by Otto Warburg. Such a switch in energy metabolisms leads to decreased generation of ATP per glucose and results in increased glucose uptake by the affected cells, a phenomenon that is widely observed through cancer imaging data. The increased accumulation of glucose is due to the fact that the outgoing rates of carbons through lactate and the electron transport chain are significantly lower than incoming rates of carbons from the glucose. The accumulated glucose/intermediates must be cleared or cells will die. Cells have evolved to adopt the process of biosynthesis to relieve this carbon burden, which gradually leads to systematic changes in cellular metabolism and ultimately results in the synthesis of new cells. This cycle accelerates as the cell population becomes increasingly more hypoxic and forms a self-propelling cycle driven by the force to remove excess carbons. This model is consistent with the large-scale transcriptomic data.

Evasion of apoptosis is one of the key hallmarks of cancer and a major target of cancer therapy. Dr. Shi-Yong Sun (Emory University) discussed death receptor 5 (DR5), a cell surface pro-apoptotic death receptor for tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). Oncogenic mutations of Ras and B-Raf frequently occur in cancer and are critical to cell transformation and tumorigenesis. In their recent study, Dr. Sun and colleagues forced expression of oncogenic Ras or B-Raf *in vitro* and demonstrated that these proteins positively regulate DR5 expression. This finding is further supported by results showing that knockdown of endogenous K-Ras or B-Raf reduced the expression of DR5. Importantly, they also showed that Ras induced DR5 expression through co-activation of the ERK/RSK and JNK signaling pathways and subsequent cooperative effects among the transcriptional factors CHOP, Elk1, and c-Jun.

In addition, Dr. Zhiren Luis Liu (Georgia State University) and Dr. Xiaole Shirley Liu (Harvard University and Dana-Farber Cancer Institute) also presented their work.

Search for Biomarkers for Cancer Subtyping, Diagnosis, and Prognosis

There were six talks on the identification and application of biomarkers. Dr. Ya-Ping Tian (Beijing 301 Hospital) described his group's study of the peripheral blood from which they identified an 8-gene panel that could be used to distinguish blood samples of hepatitis B, liver cirrhosis, and hepatocellular carcinoma patients from those of healthy donors with high statistical significance. Based on this study, they have developed a peripheral blood gene expression profiling test (GeXP) for differential diagnosis of hepatic diseases.

Dr. Chao-Nan (Miles) Qian (Van Andel Research Institute and Sun Yat-sen University Cancer Center) presented his team's finding that the secreted molecules serglycin and interleukin-8 (IL-8) promote metastasis of nasopharyngeal carcinoma (NPC) cells through autocrine and paracrine mechanisms and serve as independent prognostic factors for the survival of NPC patients. They found that IL-8 can induce the expression of many mesenchymal markers and suppress the expression of epithelial markers. Clinically, cancer cells with a high propensity for metastasis are the primary cause of patient death. However, these cells may be present in very low numbers in primary tumors, hence making gene expression profiling a major challenge. Therefore, as Dr. Qian's group demonstrated through their studies, using parental cells to isolate metastatic clones may be a useful strategy to overcome this challenge and allow identification of the pro-metastatic gene expression signature by gene expression profiling.

Dr. Bing Zhang (Vanderbilt University) discussed his group's work on identifying prognostic markers for colorectal cancer. They investigated eight published colorectal cancer gene expression signatures. Using a random walk-based approach, they integrated these signatures and publicly available somatic mutation data on a protein-protein interaction network and inferred 487 genes as plausible candidate molecular underpinnings for the colorectal cancer recurrence phenotype. The resultant list of genes was deemed an NEM signature. An NEM signature-based survival support vector machine prognostic model was trained using a gene expression dataset and tested on an independent dataset. The model-based scores were 75.7% concordant with patient survival data and separated patients into two groups with significantly different relapse-free survival (P = 0.002). Furthermore, adjuvant chemotherapy was significantly associated with prolonged survival of the high-risk patients (P = 0.006) but not beneficial to the low-risk patients (P = 0.491). Thus, the NEM signature not only reflects colorectal cancer biology but also informs patient prognosis and treatment response.

The other biomarker talks were focused on existing techniques for biomarker identification. For example, one major problem is that most biomarkers cannot be reproducibly identified by independent studies. To address this, Dr. Zheng Guo (Harbin Medical University) proposed a new strategy of using scores to evaluate the functional reproducibility of cancer biomarkers based on molecular models that take into account the functional associations among the marker genes/proteins. The biological assumption underlying a score is statistically testable to explain the diverse but functionally related biomarker genes/proteins. Dr. Guo reported that biomarkers identified using this method could be reproducibly detected when using different omic datasets.

Another serious issue is that while both molecular and network biomarkers can be used to distinguish disease samples from normal samples, neither are guaranteed to successfully identify pre-disease samples due to their static nature. Thus, these markers are not useful for early diagnosis. In a departure from traditional approaches, Dr. Luo-Nan Chen (Chinese Academy of Sciences, Shanghai) has recently developed a new theory of dynamical network biomarkers (DNBs) based on nonlinear dynamical theory and network theory. Applying this theory, Dr. Chen and his research team showed for the first time that DNBs can distinguish the pre-disease state from the normal state, even with small numbers of samples, and therefore have a great potential to achieve "real" early diagnosis of complex diseases like cancer.

Dr. Edwin Wang (National Research Council Canada and McGill University) showed that alterations of tumor suppressor genes are essential to cancer development and progression. Mutation of tumor suppressor genes often increases genomic instability, which makes passenger, or non-specific, signals more common in tumor cells than in other cell types and causes variability in the gene expression profiles between individual tumors. Thus, the "real" cancer gene expression signals may be buried in these highly varied profiles. These insights prompted Dr. Wang and colleagues to develop a new algorithm that focuses on functional modules instead of network modules, which are limited by a lack of comprehensive network data. These functional modules provide several advantages as they (1) reduce potential passenger signals; (2) overcome the well-known over-fitting problems; and (3) make the effects of the biomarkers more stable due to the functional interactions between the genes in a functional module. As proof-of-concept, they successfully applied the algorithm and identified breast cancer prognostic biomarkers that could identify low-risk patient in eight independent cohorts containing more than 1300 patients.

Dr. Shyr Yu (Vanderbilt University) also presented a talk about issues with the existing methods commonly used in bioinformatics studies and offered new solutions.

Drug Targets and Cancer Treatment Strategies

In his talk, Dr. Wei-Ping Zou (University of Michigan) focused on Th17 cells in the tumor microenvironment. Th17 cells phenotypically resemble to terminally differentiated memory T cells, but are different from central memory, exhausted and senescent T cells. His group demonstrated that Th17 cells mediate and promote long-term antitumor immunity. Furthermore, Th17 cells have stem cell-like features including high capacity of proliferative self-renewal, potent persistence and apoptotic resistance *in vivo*, and the generation of other types of T helper cells. Moreover, the stem cell-like characteristics of these cells are regulated by the signaling pathways of hypoxia-inducible factor 1α (HIF1α) and Notch. Thus, Th17 cells may be a long-lived proliferating T cell population with stem cell characteristics, which may be important determinants in Th17 biology. Therefore targeting the Th17 stemness would be therapeutically meaningful for treating patients with chronic diseases affected by Th17 cells

Electroporation is becoming a powerful and yet very simple drug delivery tool for cancer treatment. Administration of DNA encoding IL-12 has not only eradicated the directly injected melanoma tumors but also caused regression of collateral melanoma tumors in 2 out of 19 patients with in-transit melanoma in a phase I trial by Adil Daud. Dr. Shu-Lin Li (MD Anderson Cancer Center) reported that he and his colleagues generated a tumor-targeted IL-12 that is more effective than wild-type IL-12 in inhibiting metastatic tumors. He also showed results of their study in which the IL-12 gene and chemical medicine were co-administered via electroporation to treat recurrent and large-volume squamous cell carcinoma in dogs. The central hypothesis behind this co-administration approach is that chemotherapy delivered by electroporation will cause tumor cell death and release of tumor antigens, while IL-12 gene therapy delivered by electroporation will recruit and stimulate immune cells to process the released antigens to generate an antitumor immune memory. The success in causing tumor regression in dogs provides solid evidence to support this hypothesis.

Dr. Ya-Jun Guo, Dr. Xiao-Ning Wang, and Dr. Ying Gu, all from Beijing 301 Hospital, also presented their experience in treating cancers using different techniques and strategies.

Concluding Remarks

Forty years have passed since the declaration of the "war on cancer" in the early 1970s. While considerable progress has been made in our overall ability to fight this disease, cancer remains the second leading cause of death worldwide. The reality is that we are still far from reaching the goal set 40 years ago. The general consensus in the field has been that fundamentally new ways to study cancer should be developed based on the lessons learned in the past. We aimed to use this meeting series to bring together researchers who have been studying cancer from very different perspectives to develop novel views, ask deeper questions about the essence of cancer, and generate new dialogs/collaborations leading to fundamentally new understanding about cancer at the systems level.

Acknowledgments

We thank the College of Computer Science and Technology of Jilin University and the National Science Foundation of China for their funding support of the ICSB meeting series.

Received: 2012-08-08; accepted: 2012-08-17.