

Conference Report

Outsmarting cancer: an international brainstorm in Guangzhou

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Cancer is the most deadly disease in the United States. In developing countries such as China, cancer is increasingly prevalent as a cause of death. The “war against cancer” that was initially declared in the United States has become a global war that requires an alliance of world-wide cancer researchers. As part of such an effort, the Second Guangzhou International Symposium on Oncology was held on May 20-22, 2011, in Guangzhou, China. The symposium was jointly organized by the Guangdong Anti-Cancer Association, the US Chinese Anti-Cancer Association (USCACA), the *Chinese Journal of Cancer*, and the Sun Yat-sen University Cancer Center. More than 1000 cancer researchers attended, including speakers from China, the USA, Finland, England, Japan, and Spain. The presentations covered most cancer types and both basic and clinical research. Recurring themes of the presentations were that cancer is “smart”, cancer is complex, and cancer cells communicate actively. Outsmarting cancer is clearly a challenging task that needs multipronged attacks on multiple targets and on the communication systems among cancer cells. Presenters and attendees left the conference with a sense of urgency in the need for more communication among cancer researchers in fighting this disease.

In this article, we summarize highlights from a number of presentations. Many of the presenters have published or will publish reviews and research articles in the *Chinese Journal of Cancer*, which has become an important international forum in disseminating exciting cancer research progress.

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doi: 10.5732/cjc.011.10268

Tumors Are Smart in Maintaining Heterogeneity

Cancer is a highly heterogeneous disease involving multiple genetic and epigenetic alterations. However, the molecular mechanism for maintaining tumor heterogeneity is unclear. Webster K. Cavenee reported that a relatively small number of glioblastoma cells harboring mutated epidermal growth factor receptor (EGFR) can secrete interleukin-6 and promote growth of neighboring tumor cells that have wild-type EGFR. This paracrine mechanism illustrates an effective crosstalk among cancer cells with different properties and thus helping maintain tumor heterogeneity. The study suggests the importance of targeting cancer communication with therapeutics.

Understanding Tumor Heterogeneity

The identification of driving genetic events for each subtype of cancer will be a critical step in the realization of personalized targeted medicine. A significant milestone development in this effort is the ongoing project of The Cancer Genome Atlas (TCGA), funded by the US National Cancer Institute (NCI). The goal of TCGA is to map all genomic alterations in 500 patient samples for more than 20 major cancer types. Wei Zhang, a co-director of a Genome Data Analysis Center under TCGA, presented recent results from the ovarian cancer project. Ovarian cancer is the leading cause of death from gynecologic malignancies among women in western countries. The lethality of ovarian cancer is due to its high rate of metastasis and drug resistance. Therefore, one of the most important challenges in treating ovarian cancers and improving survival is to identify effective therapeutic targets.

Toward this goal, ovarian cancer is one of the first two cancer types that have gone through comprehensive genomic characterization under TCGA. Zhang presented their analysis of the different roles of *BRCA1* and *BRCA2* mutations in ovarian cancer prognosis (survival and resistance to therapy). Zhang also presented an integrated analysis of microRNAs and protein-coding

genes in identifying a mesenchymal subtype of ovarian cancer that is associated with metastasis and shorter survival.

Integrated network analysis to uncover cancer dysregulation depends on effective computational models. Olli Yli-Harja and Matti Nykter presented their work using computational modeling and systems biology approaches to uncover key nodes (potential targets) for several cancer types including glioblastoma and sarcoma.

Tumor Microenvironment Is Crucial

Tumor microenvironment has been increasingly recognized as essential for tumor development and progression, but the cellular components and signaling characteristics are not fully understood in various malignancies. Jingwu Xie discussed the importance of hedgehog (Hh) signaling in both the tumor and the stromal compartments in pancreatic cancer. While tumor-specific Hh signaling is required for distal metastasis, stromal Hh signaling is required for tumor growth. Xie suggested that for patients with stromal activation of Hh signaling, SMO-specific Hh inhibitors should be effective, whereas patients with tumor-specific activation of Hh signaling require treatment with Gli inhibitors.

Erwei Song reported a new discovery that tumor-associated macrophages in breast cancer can secrete the cytokine CCL18, and that CCL18 can bind to the membrane-associated phosphatidylinositol transfer protein 3 (PITPNM3) of tumor cells. This promotes the epithelial-mesenchymal transition of tumor cells and induces invasiveness in breast cancer cells.

Novel Oncogene in Glioblastoma

Glioma is the most common type of brain tumor. The most advanced glioma, glioblastoma, is one of the worst cancer types: patient survival is just over a year after diagnosis and has not significantly improved for the past 40 years. Identifying new therapeutic targets for glioma is an urgent need. Lynette Moore presented the discovery and characterization of insulin-like growth factor-binding protein 2 (*IGFBP2*) as a novel oncogene for glioma. Using a powerful glia-specific transgenic mouse model, Moore presented evidence that *IGFBP2* is a driver oncogene for glioma. An inducible system showed that inactivation of *IGFBP2* led to repression of glioma and increased survival. Thus, *IGFBP2* is needed for maintenance of glioma and as such is a

therapeutic target.

Tyrosine Kinase Inhibitor (TKI)-targeted Therapy

Targeting mutated EGFR has been shown to be effective against several types of solid cancer in preclinical studies, including non-small cell lung cancer (NSCLC) and glioma. The high incidence rate of EGFR-activating mutations in Asian populations has made Asian lung cancer patients more suitable for targeted therapy using a tyrosine kinase inhibitor (TKI) specifically blocking EGFR functions. Toshihiro Nukiwa reported promising treatment outcomes in Japanese patients with NSCLC.

Mutated EGFR has also been found to be essential for the maintenance of glioma. However, some glioma cells survive well even after blocking of EGFR signaling. Jill E. Wukosky introduced a newly found protein, KLHDC8A (or SDE1), that enables glioma cells to escape from EGFR targeting by TKI. Identifying the escape mechanisms and the key molecules that are responsible is critical for the design of therapeutics that will follow front-line treatment.

Novel Approaches to Target Cancer

A promising anti-cancer strategy presented by Peng Huang is based on the abnormality of the mitochondrial respiratory chain in cancer cells. The intrinsic increased generation of reactive oxygen species (ROS) in cancer cells induces redox adaptation in response to the sustained oxidative stress, leading to an up-regulation of glutathione (GSH) and other antioxidant molecules that are essential for cancer cell survival. We can selectively kill cancer cells using compounds such as phenethyl isothiocyanate and buthionine sulfoximine, which disable the GSH antioxidant system by depletion of cellular GSH and inhibition of important redox-modulating enzymes such as glutathione peroxidase.

In another approach, some old drugs might bring new hope to the anti-cancer war. The inhibitors of type 5 phosphodiesterase (PDE-5) were recently found to be able to enhance the anti-cancer effect of paclitaxel by blocking ATP-binding cassette transporters, which is a protein family that can pump out cytotoxic drugs and induce drug resistance. Zhe-Sheng Chen showed some promising data for combined therapy using sildenafil (Viagra, a PDE-5 inhibitor) and paclitaxel.

Advances in Radiotherapy

In recent years, great advances have been made in

traditional photon radiotherapy. Joe Y. Zhang summarized these advances in image-guided radiation therapy (IGRT), stereotactic body radiotherapy (SBRT), and intensity-modulated radiation therapy (IMRT), which provide personalized adaptive radiotherapy that improves local control and survival with reduced toxicity. The promising advantages of charged particle radiotherapy were also discussed by Guo-Liang Jiang. The rapid development of the facilities around the world for proton and heavy-ion radiotherapy has sparked hope for better control of localized tumors.

Personalized Medicine Needs Predictive and Prognostic Markers

Personalized medicine was a hot topic at this symposium. Andres Cervantes introduced his experience in applying a personalized approach to treating advanced colon cancer. Dongfeng Tan discussed the challenges

and opportunities of molecular/genomic testing for personalized medicine. Identifying and validating biomarkers for targeted therapy has been recognized as crucial in developing personalized medicine. Tomohide Tamura discussed the current phase I trial in Japan for identifying effective biomarkers. Li Yan's presentation indicated that a biomarker-driven approach for anti-cancer drug development has been adopted in major pharmaceutical companies.

Regarding novel predictive and prognostic markers for personalized medicine, microRNAs, with their high stability, emerge as a major class of molecules with promising potential in cancer diagnosis, prognosis prediction, and treatment response monitoring. William C.S. Cho presented advances in microRNA research. Meng-Feng Li reported that miR30e* directly targets and suppresses I κ B α expression in glioma and activates NF- κ B signaling and downstream gene expression that are important for cancer invasion and angiogenesis.