NUS National University of Singapore | Department of Biological Sciences Faculty of Science

SEMINAR

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Hosted by A/P Liou Yih Cherng

Marker-guided targeted therapy, PARP inhibitors, and immune checkpoint therapy

Mien-Chie Hung, Ph.D. is vice president for basic research and professor and chair of the Department of Molecular and Cellular Oncology. He received undergraduate and graduate degrees from the National Taiwan University and his PhD from Brandeis University. After completing postdoctoral training with Dr. Robert A. Weinberg at the Whitehead Institute/Massachusetts Institute of Technology. Dr. Hung was recruited to MD Anderson in 1986. Dr. Hung is internationally recognized for his studies of signal transduction pathways regulated by tyrosine kinase growth factor receptors, such as EGFR and HER-2/neu, as well as molecular mechanisms of tumorigenesis. Up to date, Dr. Hung has published 485 peer-reviewed articles and his lifetime h-index is 109. Dr. Hung has served in many study sections of the NIH and various funding agencies in many other countries to select awardees. He is one of members of Selection Committee for Tang Prize in Biopharmaceutical Science category and 2016 Pezcoller Foundation-AACR Award. Dr. Hung also serves as an editorial member for many journals in cancer research to evaluate quality of submission. Notable, he is one of the founding Editorial Members for Cancer Cell and Editor-in-chief for American Journal for Cancer Research. Dr. Hung was inducted as an Academician of the Academia Sinica in Taiwan in 2002. In addition, Dr. Hung was selected as a Fellow in Biological Sciences section, American Association for the Advancement of Science in 2010. Dr. Hung is a basic scientist with a keen translational vision and especially his recent research effort has significantly contributed to understanding the biology of cancer and to developing combinational cancer therapies to overcome resistance. His laboratory has a long term commitment to 1) discovery of novel functionality of epidermal growth factor receptor (EGFR) family which may provide useful insight to understand cancer formation and development; 2) identification of crosstalks of signal pathways/networks in cancer cells and tumor microenvironment which could potentially predict resistance to target therapy; and 3) development of marker-guided targeted therapy which will effectively treat cancer patients.

By **Mien-Chie Hung**

Vice president for basic research and professor and chair of the Department of Molecular and Cellular Oncology, MD Anderson Cancer Centre, The University of Texas, USA

Poly (ADP-ribose) polymerase (PARP) inhibitors have emerged as promising therapeutics for many diseases, including cancer, in clinical trials. Three PARP inhibitors have been approved by the FDA to treat ovarian cancer with (olaparib and rucaparib)or without BRCA mutations (niraparib). BRCA1 and BRCA2 play essential roles in repairing DNA double strand breaks, and a deficiency of BRCA proteins sensitizes cancer cells to PARP inhibition. My group recently demonstrated that receptor tyrosine kinase c-Met associates with and phosphorylates PARP1 at Tyr907. Phosphorylation of PARP1 Tyr907 increases PARP1 enzymatic activity and reduces binding to a PARP inhibitor, thereby rendering cancer cells resistant to PARP inhibition. Combining c-Met and PARP1 inhibitors synergized to suppress growth of breast cancer cells in vitro and xenograft tumor models. Similar synergistic effects were observed in a lung cancer xenograft tumor model. These results suggest that PARP1 pTyr907 abundance may predict tumor resistance to PARP inhibitors, and that treatment with a combination of c-Met and PARP inhibitors may benefit patients bearing tumors with high c-Met expression who do not respond to PARP inhibition alone (Nature Medicine 22:194-201, 2016).

Extracellular interaction between programmed death ligand-1 (PD-L1) and programmed cell death protein-1 (PD-1) leads to tumor-associated immune escape. Here, we show that the immunosuppression activity of PD-L1 is stringently modulated by ubiquitination and N-glycosylation. We identified glycogen synthase kinase 3b (GSK3b) as a novel protein that interacts with PD-L1 and can induce phosphorylation-dependent proteasome degradation by b-TrCP. We also demonstrate that epidermal growth factor (EGF) stabilizes PD-L1 via GSK3b inactivation in basal-like breast cancer (BLBC). Inhibition of EGF signaling by gefitinib destabilizes PD-L1, enhances antitumor T cell immunity and therapeutic efficacy of PD-1 blockade in syngeneic mice models. Together, we demonstrated a novel interchange between glycosylation and phosphorylation regulating ubiquitination and degradation of PD-L1. This regulatory event is critical for BLBC cells that escape immune surveillance via PD-L1/PD-1 interaction. Importantly, inhibition of EGF-mediated PD-L1 stabilization enhances a therapeutic efficacy of PD-1 blockade to promote tumor-infiltrating cytotoxic T cell immune response. Thus, targeting PD-L1 stabilization provides a novel strategy to combat BLBC-mediated immunosuppression and may potentially apply to other cancer types (Nature Communications 7:12632, 2016). In a most recent study, we identified TNFα as a major factor triggering cancer cell immunosuppression against T cell surveillance via stabilization of programmed cell death-ligand 1 (PD-L1) (Cancer Cell, 30:925, 2016). To this end, in collaboration with StCube Pharmaceuticals Inc., we have developed monoclonal antibodies against glycosylation-specific PD-L1. Impressive therapeutic effect was observed through ab-drug-conjugate approach and a manuscript is in press in Cancer Cell.

Artwork by Ann Nee, DBS, NUS