香港城市大學
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電腦科學系
Department of
Computer Science

COMPUTER SCIENCE COLLOQUIUM

Uncovering Drug Targets and Paired Markers in Cancer

SPEAKER **Dr Grace S. Shieh**

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DATE 20 December 2018(Thursday)
TIME 4:00 pm - 5:00 pm
VENUE CS Seminar Room, Y6405
6th Floor, Yellow Zone
Yeung Kin Man Academic Building
City University of Hong Kong
83 Tat Chee Avenue
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ABSTRACT

Targeting synthetic lethal (SL) partners of mutated cancer genes will specifically kill cancer cells bearing the mutations but spare normal cells. Therefore, for non-druggable mutant tumor suppressor genes and oncogenes, e.g. TP53 and KRAS, synthetic lethality strategy offers an elegant alternative.

Two genes are said to have synthetic lethal (SL) interaction if their simultaneous mutations lead to cell death, but each individual mutation does not. Using synthetic lethality-based methods to develop cancer-specific therapeutics has been rapidly adapted due to its translational impact. Here, we present an integrated approach to uncover drug targets and paired prognostic markers in colorectal cancer (CRC) and lung adenocarcinoma (LADC).

This approach used 660+ collected verified SL pairs, microarray gene expression data, protein levels (immunohistochemistry staining) of ~20 selected genes and clinical features of 171/130+ CRC/LADC patients. This method resulted in 11 predicted SL pairs for CRC, including MSH2-POLB and CSNK1E-MYC previously verified in CRC. Additionally we validated CSNK1E-TP53 and CTNNB1-TP53 using RNAi and small-molecule inhibitors, and the former via mouse model. Further, CSNK1E-TP53, CTNNB1-TP53 and two other protein pairs are shown to be markers for CRC patient survival.

For LADC, of the 20+ predicted SL pairs, four pairs are consistent with literature and the synthetic lethality of TP53-PARP1 was validated in CL1-5 and H1975 cells. RAD54B ↑ , BRCA1 ↓ -RAD54B ↑ , FEN1(N) ↑ -RAD54B ↑ and PARP1 ↑ -RAD54B ↑ were revealed to be prognosis (predictive) markers, independent from age and stage. Further, these markers were confirmed by three external gene expression data sets. Finally, some future research questions will be discussed.

The results on CRC and LADC were published in Neoplasia (2014) and Oncotarget (2016), respectively.

BIOGRAPHY

Dr Grace S. Shieh is a Full Research Fellow at Institute of Statistical Science in Academia Sinica. Before joining Academia Sinica, she was a faculty member at University of Missouri. She obtained her Ph.D. in Statistics from University of Wisconsin-Madison and B.Sc. in Mathematics from National Taiwan University (NTU). She is also a core faculty member of genome and systems biology for NTU & Academia Sinica. She is an elected member at International Statistical Institute. She is an associate editor for multiple international journals and have published extensively across different disciplines. For now, she is interested in disease bioinformatics.

All are welcome!

In case of questions, please contact Dr WONG Ka Chun at Tel: 3442 8618, E-mail: kc.w@cityu.edu.hk, or visit the CS Departmental Seminar Web at http://www.cs.cityu.edu.hk/.