國立中山大學應用數學系
學術演講

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講　題：Uncovering drug targets and paired markers in cancer
時　間：2018/11/29（星期四）14:10 ~ 15:00
地　點：理學院四樓理 SC 4009-1 室
茶　會：15:00 於理 SC 4010 室 (系辦公室)

摘 要

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.

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