Cancer Science Institute of Singapore

Research Meeting

Date: Friday, 22 May 2015
Time: 12pm – 1pm
Venue: LT36, Level 3 Auditorium, MD6
14 Medical Drive, Singapore 117599

Ricky Lim

Research Assistant, Dr. Touati Benoukraf's group

Chromatin Conformation Prediction from ChIPseq signal.

Chromatin Immunoprecipitation followed by sequencing (ChIP-seq) has gained growing popularity in last few years. This can be seen from increasing amount of ChIP-seq data generated. Conventionally ChIP-seq data has been analyzed to identify DNA binding sites of a protein of interest in a rather two-dimensional fashion. However, a protein rarely functions alone but work together with other proteins within a complex to precisely control the function of the target binding sites. Furthermore, the three-dimensional cellular context provides the clue to interpret ChIP-seq data in a rather three-dimensional fashion. The needs remain strong for methods to improve the interpretation of ChIP-seq data to characterize binding sites of a protein of interest. Here, we are developing a set of methods to improve the interpretation of ChIP-seq signals. We introduce a probabilistic clustering methods to segregate the direct and indirect binding sites of the protein complex. Following the segregation, we will apply a functional annotation of the identified protein complex based on the cluster of binding sites, instead of single binding sites. We believe that our set of methods will empower ChIPseq data interpretations to better understand the mechanisms of co-regulations.

Wang Tingting

Research Pathologist, Dr. Lee Soo Chin's group

Simvastatin exerted anti-tumoral effects through deactivating PI3K/Akt/mTOR and MAPK/ERK pathways in breast cancer via inhibiting mevalonate pathway

Statins purportedly exert anti-tumoral effects on breast cancer. However, the biologic mechanisms for these actions are not fully elucidated. The aims of this study were 1) to explore the effects of simvastatin on apoptosis, proliferation and commonly abrogated pathways, including PI3K/Akt/mTOR and MAPK/ERK, in a window-of-opportunity breast cancer trial; 2) to further confirm findings from the clinical trial by functional studies. In clinical samples, simvastatin led to increase in cleaved caspase-3 and decreased trend for Ki67. Simvastatin markedly suppressed PI3K/Akt/mTOR signalling by activating PTEN and by dephosphorylating Akt and S6RP; it also inhibited MAPK/ERK pathway by dephosphorylating c-Raf and ERK1/2. In breast cancer cells MCF-7, MDA-MB-231 and BT-549, simvastatin treatment consistently induced apoptosis and inhibited proliferation by deregulating caspase cascades and cell cycle proteins in a dose dependent manner. Concordantly, simvastatin strongly suppressed PI3K/Akt/mTOR pathway by enhancing PTEN expression and by further sequentially dephosphorylating downstream cascades including Akt, mTOR, p70S6K, S6RP and 4E-BP1. Furthermore, simvastatin significantly inhibited MAPK/ERK pathway by dephosphorylating sequential cascades such as c-Raf, MEK1/2 and ERK1/2. Simvastatin-induced anti-tumoral effects and deactivation of PI3K/Akt and MAPK/ERK signallings were reversed by metabolic products of the mevalonate pathway, such as mevalonate, farnesyl pyrophosphate and geranylgeranyl pyrophosphate. Simvastatin promoted apoptosis and suppressed proliferation by deactivating PI3K/Akt/mTOR and MAPK/ERK signalling through inhibition of mevalonate pathway. These findings shed light on the biological and potential anti-tumor effects of simvastatin in breast cancer.