Cancer Science Institute of Singapore

Research Meeting

Date: Friday, 8 May 2015
Time: 12pm – 1pm
Venue: LT36, Level 3 Auditorium, MD6
14 Medical Drive, Singapore 117599

Nicolas Bertin

Senior Research Scientist, Asst Prof. Melissa Fullwood's group

De-orphanizing non-coding somatic mutations in cancers with chromatin interactions by ChIA-PET

Somatic alterations of the genome are a leading cause of cancer development and progression. While, advances in sequencing technologies have enabled the discovery of alterations in protein-coding genes in large cohorts of cancer-derived samples, genome-wide surveys of somatic alterations also revealed that a subsequent amount of mutations in cancers also cluster within non-coding regions of the genome. In contrast to alterations of protein-coding genes, the consequences of which can be understood in terms of modifications of the protein integrity and function, unravelling the implications of somatic mutations in non-coding and intergenic regions of the genome has remained a challenge. Within cell nuclei, the genome is compactly folded. Chromatin Interaction Analysis with Paired-End Tag (ChIA-PET) has been employed to systematically analyze genome-wide chromatin folding. These studies allowed the linking of enhancer regions associated with disease by Genome-Wide Association Studies (GWAS) to their target genes through chromatin interactions. Similarly, we hypothesize that a subset of intergenic somatic mutations arises in enhancer regions affecting distant genes through chromatin interactions, thus perturbing their proper transcription. Addressing the bioinformatics challenges of the latest improvements in the ChIA-PET protocol, we have developed ChIA-PETTER, a new, robust method of calling chromatin interactions. We have also used ChIA-PETTER to reprocess all the published chromatin interaction libraries to-date, creating a large resource of chromatin interactions detected in breast and blood cancer derived cell lines genomes. We, then, combined this resource with a collection of genome-wide somatic mutation hotspots compiled from whole-genome sequencing based surveys by The Cancer Genome Atlas consortium in, amongst others, leukemia and breast cancer. Strikingly, we identified thousands of chromatin loops between distant intergenic somatic mutation hotspots and known genes promoter regions in the model cancer cell lines K562, GM12878 (leukemia) and MCF-7 (breast carcinoma), indicating that many somatic mutations could potentially function through chromatin interactions. In further work, to gain insights into the potential function of those mutated region we are integrating the available gene expression profiling from a subset of breast cancer patient for which somatic alteration had been surveyed and the large genome-wide transcription factor binding and histone modification surveys by ENCODE in MCF-7.

Li Jia

PhD Student, A/Prof. Henry Yang & Prof. Phillip Koeffler's group

Epigenetic aberrations in clear cell renal cell carcinoma

ZRSR2 is a spliceosome gene, located on X-chromosome, and frequently mutated in Myelodysplastic Syndrome (MDS). This splice factor is involved in recognition of 3'-splice site during the early stages of spliceosome assembly. However, its precise role in RNA splicing has remained unclear. To understand the splicing changes due to the mutations of ZRSR2 in MDS, we developed a bioinformatics pipeline for identification of aberrant splicing using RNA-seq data. We analyzed splicing in MDS bone marrow with and without ZRSR2 mutations as well as normal bone marrow. We identified increased mis-splicing in ZRSR2 mutant MDS compared to ZRSR2 wild-type samples. Aberrant splicing was consistently detected across different mutant samples and invariably affected the U12-type introns. These results were also validated experimentally using realtime PCR and Sanger sequencing. Our analysis pipeline was also useful to categorize the splicing defects as intron retention, usage of cryptic 5'/3' splice sites or exon skipping. This computation approach predicted splicing alterations in pairwise comparisons with high confidence and can be used for global analysis of differential splicing. These findings underline the important role of ZRSR2 in RNA splicing and highlight dysregulated splicing of U12-type introns as a distinctive feature of ZRSR2 mutations in MDS.