RNA Salon Singapore

With support from:

20 min talks from ECRs followed by snacks and networking

Feb 12th 4:00 - 6:00 pm

Genome Institute of Singapore, L2

Single-cell RNA-seq links cell-type-specific regulation of splicing with complex diseases

Tian Chi, National University of Singapore

Synopsis: Alternative splicing is a critical intracellular process that links genetic and environmental variation to complex traits and diseases. While previous studies have predominantly focused on bulk tissues, revealing tissue-specific splicing regulation, splicing regulation at the cell-type level remains incompletely understood. In addition, most functional genomic studies have focused on European populations, leaving Asian populations substantially under-represented. Here, we analyzed alternative splicing in approximately one million peripheral blood mononuclear cells from 474 healthy donors using the Asian Immune Diversity Atlas single-cell RNA-seq dataset. We identified widespread sex- and ancestry-biased differential splicing, the majority of which is cell-type-specific. By integrating genotype data, we mapped 11,577 independent cis-sQTLs, 607 trans-sGenes, and 107 dynamic sQTLs. Colocalization analysis between cis-eQTLs and trans-sQTLs revealed a cell-type-specific regulatory relationship between hnRNPLL and PTPRC. We further observed strong enrichment of cis-sQTL effects in autoimmune and inflammatory disease heritability. Notably, we functionally validated an Asian-specific sQTL disrupting the 5′ splice site of TCHP exon 4, which may modulate Graves' disease risk in East Asian populations. Together, this work underscores the importance of ancestral diversity and provides a roadmap for dissecting splicing mechanisms in complex diseases at single-cell resolution.

Cryo-EM structures of anti Z-DNA antibodies in complex with antigen reveal distinct recognition modes of a left-handed geometry

Danielle Chin Huey Ren, Nanyang Technological University

Synopsis: Double-stranded nucleic acids can undergo transitions from canonical B/A-forms to alternate left-handed Z-DNA/Z-RNA (Z-NAs). Z-NAs are implicated in processes such as neuroinflammation in Alzheimer's disease, Lupus Erythematosus, microbial biofilms, and type I interferon-mediated human pathologies. Since endogenous Z-NA sensors like the Zα domain can induce B-to-Z transitions, monoclonal antibodies (mAbs) Z-D11 and Z22 have been regarded as conformation-specific tools to confirm Z-NA in situ, although high-resolution structural information is missing. Here, we employed single-particle cryo-electron microscopy to solve structures of Z-D11 and Z22 bound to synthetic d(CG)6 12mer Z-DNA duplex. Both mAbs form filamentous trimers around the Z-DNA axis, further stabilized by Fab-Fab interactions. The mAbs achieve specificity through extensive contacts to both Z-form backbone strands and the exposed guanine/cytosine bases in the major groove. This mode of recognition is dictated by shape complementarity rather than sequence specificity, sensing the alternating syn/anti backbone torsions and the phosphate zig-zag geometry unique to Z-DNA. Our data also suggest that these mAbs are not inducing B-to-Z transitions under normal physiological conditions. Finally, comparison to other double-stranded NA-binding mAbs defines a similar structural logic adapted to different helical geometry recognition patterns, thus providing a framework for engineering highly specific nucleic acid probes.

Prot2RNA: Protein-Conditioned mRNA Design with Generative Models

Ivona Martinovic, Genome Institute of Singapore

Synopsis: The redundancy of the genetic code allows many mRNA coding sequences to encode the same protein, yet synonymous codon choices can strongly influence mRNA stability, structure, and translation. Designing mRNA sequences that respect both protein sequence and biological constraints remains challenging.

In this talk, I will present Prot2RNA, a generative model for protein-conditioned mRNA design. In the current version, Prot2RNA enables exploration of diverse synonymous coding sequences consistent with a target protein and captures biologically meaningful codon preferences beyond simple frequency matching. I will discuss initial results on human mRNA data and highlight ongoing efforts to incorporate additional biological signals into the generation process.