DEPARTMENTAL SEMINAR SERIES

Molecular Genetics
UNIVERSITY OF TORONTO

Temerty Medicine

Molecular innovation at the CRISPR-transposon interface

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CRISPR-Cas systems protect bacteria and archaea from foreign invaders, including viruses and plasmids. Paradoxically, though, CRISPR-Cas evolution involved the repeated co-option of genes from another major class of mobile genetic elements: transposons. Transposon-encoded tnpB genes encode RNA-guided DNA nucleases that promote their own selfish spread through cut-and-copy recombination, and this widespread gene family was repeatedly domesticated over evolutionary timescales, leading to the emergence of diverse CRISPR-associated nucleases including Cas9 and Cas12. We set out to test the hypothesis that TnpB nucleases may have also been repurposed for novel, unexpected functions other than CRISPR-Cas. Here, using phylogenetics, structural predictions, comparative genomics, and functional assays, we uncover multiple instances of programmable transcription factors that we name TnpB-like nuclease-dead repressors (TldR). These proteins employ naturally occurring guide RNAs to specifically target conserved promoter regions of the genome, leading to potent gene repression in a mechanism akin to CRISPRi technologies invented by humans. Focusing on a TldR clade found broadly in Enterobacteriaceae, we discover that bacteriophages exploit the combined action of TldR and an adjacently encoded phage gene to alter the expression and composition of the host flagellar assembly, a transformation with the potential to impact motility, phage susceptibility, and host immunity. Our work showcases the diverse molecular innovations that were enabled through repeated exaptation of genes encoded by transposable elements, and reveals that RNA-guided transcription factors emerged long before the development of dCas9-based editors.

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