CHRISTOPHER KEOWN'S DEFENSE

GENOME-SCALE STUDIES OF DYNAMIC DNA METHYLATION IN MAMMALIAN BRAIN CELLS

ABSTRACT:

Developmental processes, genes and environmental factors interact to produce changes in cognition and behavior over the lifespan of an individual. However, the underlying molecular genetic mechanisms that mediate these changes remain to be fully elucidated. DNA methylation is an epigenetic mechanism that defines cell identity and helps regulate gene expression. DNA methylation is dynamic over development and has been shown to mediate experience-dependent changes, including those resulting from learning and memory and early life adversity. Although methylation mainly occurs at genomic cytosines in the CG dinucleotide context, methylation at non-CG sites was recently found in brain tissue. Non-CG methylation is specifically enriched in neurons and accumulates during the early childhood stages of brain development. The biological impact of non-CG methylation in regulating gene expression and regulating cellular function, if any, remains unclear. A major challenge for addressing this question is the complexity and scale of the DNA methylation landscape, which includes nearly one billion cytosines throughout the genome that are potential sites of modification in every cell. Targeted studies of specific candidate genes and genomic loci do not elucidate the overall configuration of the cellular epigenome. Techniques for comprehensively mapping the genome-wide distribution of DNA methylation are powerful, but they require sophisticated new computational methods of analysis that can reliably distinguish and statistically validate epigenomic differences related to developmental and environmental factors.

In this thesis we develop new approaches to comprehensively analyze DNA methylation throughout the genome and with single base resolution in order to better characterize the role of CG methylation and elucidate the potential role of CH methylation in mammalian brain cells. First, we consider the impact of enriched early life (peri-pubertal) experience on DNA methylation and gene expression in the dentate gyrus of the hippocampus. In addition to its role in experience-dependent gene regulation, DNA methylation also plays a key role in innate developmental processes, including female X chromosome inactivation. We provide the first allele-specific DNA methylomes from the active and inactive X chromosomes in female brain, and use comprehensive genomic analyses to gain insight into the functional relationship between allele-specific DNA methylation and transcription. These two studies provide new evidence of the dynamic changes in DNA methylation in whole brain tissue caused by environmental and innate developmental factors. However, they do not address the heterogeneity of brain cell types, a hallmark of mammalian brain organization. To address the role of DNA methylation in brain cell diversity, we develop computational methods to analyze data from a new assay that measures single cell methylomes. Using these data, we show that brain cell methylomes can be clustered and used to assess neuronal heterogeneity in the frontal cortex of mouse and human. Upon clustering cells, we are able to gain insight into the role of methylation in the establishment and maintenance of cellular identity in neuronal types.

Overall, this thesis adds to the increasing evidence that DNA methylation is a cell type-specific, dynamic epigenomic modification of brain cells that is impacted by, and may in turn help to regulate, neuronal development and adaptation. In addition, this thesis provides new computational methods for analyzing large-scale, whole-genome DNA methylation data sets and demonstrates their use in uncovering new insights into the mammalian brain epigenome.

CHRISTOPHER KEOWN TO DEFEND

MONDAY, JUNE 4TH, 2018 AT 10:00AM

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