

Stem & Progenitor Cell Interest Group

Wednesday, February 13, 2019

Kelly Barnett

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“Capturing spatiotemporal dynamics of DNA methylation across the chromatin accessible genome during cell fate specification”

"While DNA methylation (DNAm) patterns are highly dynamic and cell-type specific at enhancers, current models inadequately describe the role of DNAm within the ordered process of enhancer activation and cell differentiation, both frequently perturbed in human disease. DNAm is suggested to be crucial for cell differentiation, as stem and progenitor cells defective for DNAm pathways demonstrate impaired cell differentiation. Previously, we identified a class of non-coding genomic regions among the methylomes of discrete hematopoietic cell types that appear to undergo progressive DNA demethylation across cell fates. Intriguingly, many of these same genomic regions while methylated, exist in nucleosome-depleted genomic regions. This led to a hypothesis that chromatin accessibility (ChrAc) and DNAm dynamics are separate molecular events representing distinct stages of enhancer activation. Thus, we developed a method (ATAC-Me) to probe ChrAc and DNAm from a single DNA library by coupling assay for transposase accessible chromatin (ATAC) with subsequent bisulfite conversion. We have applied ATAC-Me across a THP1 monocyte to macrophage cell differentiation time course. We identified multiple waves of ChrAc changes decoupled from DNAm changes supporting that concomitant ChrAc and DNAm are a unique enhancer activation stage. In contrast, we observed ChrAc dynamics and nearby transcriptional responses remain coupled regardless of intergenic DNAm state. Further, transcription factor (TF) footprints were effectively ascertained from ATAC-Me, and enriched for TF motifs corresponding to distinct ChrAc and gene regulatory responses. Collectively the ATAC-Me methodology offers a new tool to characterize the DNAm and ChrAc relationship in a multitude of contexts. In this work we have applied ATAC-Me to construct a timeline for enhancer activation events, namely, ChrAc and transcriptional dynamics preceding DNAm changes across cell differentiation."



9:00 am – 9455 MRB IV

Bagels provided