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506.BONE MARROW MICROENVIRONMENT

Gene Regulatory Networks Controlling Sinusoidal Hematopoietic Niche Function

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The bone marrow sinusoidal vascular niche is important for HSC engraftment and regeneration of hematopoiesis after transplantation, but the epigenetic factors that control these biological functions are undefined. Here, we show that sinusoidal hematopoietic niche functions are controlled by gene regulatory networks (GRNs), involving transcription factors (TFs) that bind to enhancers to regulate corresponding target genes.

To characterize sinusoidal niche specific transcriptional and chromatin accessibility states, we performed multimodal single nuclei RNA and ATAC-seq analysis on unsorted zebrafish embryos. We identified 4 niche clusters, including mesenchymal stem cells, fibroblasts, osteoblasts and sinusoidal endothelial cells. Differential RNA transcriptome analysis confirmed the identity of each niche cluster with canonical gene markers for each niche cluster. To examine differential transcriptional accessibility in zebrafish niche clusters, we aggregated co-accessible regions in cells from these clusters. Each cluster demonstrated a unique chromatin accessibility profile with differentially accessible regions. Differential motif activity based on chromatin accessibility analysis further exhibited unique TF motifs activity in sinusoidal endothelial cells.

To identify potential regulatory TFs in sinusoidal vascular niche, we predicted TFs based on the TF binding sites accessibility and TF expression. Thus, we identified 3 specific expressed and enriched TFs for sinusoidal vascular niche, including Fli1 (Friend leukemia integration 1), Mef2a (Myocyte enhancer factor 2A) and Mef2c. Next, to investigate genomic regulatory regions that interact with TFs, in which control the transcription of their target genes, we performed random forests and regression trees machine learning methods to infer GRNs. We observed multiple active GRNs in sinusoidal vascular niche, which were predicted to essential for regulating hematopoietic niche development and HSC maintenance, including klf12, egfl7, ebf3 and ldb2.

Finally, we examined whether these putative gene regulatory networks were conserved across species and tissue types. We used same approach (single-cell multiome sequencing) on E4-HUVEC cells, a transduced human umbilical vein endothelial cells (HUVEC) with the adenovirus E4ORF1 gene, which was a well-defined model of the human sinusoidal vascular niche. We likewise observed regulatory networks in HUVEC cells. As in zebrafish, GRNs in human sinusoidal cluster consisted of FLI1 and MEF2 family, regulatory regions and their target genes. Our findings reveal that unique sinusoidal vascular niche specific gene regulatory networks, including TFs, regulatory regions and target genes indicate the treatments targeting GRNs may help to facilitate reprogramming of sinusoidal endothelial niche to support HSC homing and regeneration after transplantation.

Disclosures No relevant conflicts of interest to declare.

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