Hoxa1-TALE Gene interaction network regulates TALE cofactors, signaling pathways and pluripotency during neural differentiation

Bony De Kumar[1], Hugo Parker[1], Mark Parrish[1], Ariel Paulson[1], Julia Zeitlinger[1,2] and Robb Krumlauf[1,2]

[1] Stowers Institute for Medical Research, Kansas City, 64110
[2] The University of Kansas School of Medicine.

ABSTRACT

Hox genes are key regulators of hierarchical gene interaction networks involved in patterning of early embryonic development thorough input into control of cellular identity. Specificity of Hox gene binding is attributed to Co-factors and interactors. Interestingly, functional roles of Hox genes are believed to be mediated through combinatorial activities of Hox genes along anterior posterior body axis. This combinatorial Hox code likely reflects a balance of inputs into downstream target genes by individual Hox proteins and their cofactors targets or multiple Hox proteins and cofactors set up by the nested domains of gene expression. Among many characterized co-factors of Hox genes, TALE (Three amino acid loop extension) homeodomain proteins represent a group of proteins that include some the previously characterized Hox cofactors Pbx and Meis. The TALE group of transcription factors consists of six protein families namely IRX, MKX, MEIS, PBC, PKNOX and TGIF which are implicated in many developmental and disease processes. We used programmed differentiation of mouse ES cells into a neural like identity and genomic approaches to investigate the underlying gene interaction network regulated by Hoxa1 and its TALE cofactors. This has provided insight into downstream targets of Hoxa1. Analysis of genes near Hoxa1 bound regions shows enrichment of genes involved in major signaling pathways, including: TGF-beta, WNT, Hedgehog and Hippo pathways and processes depending on inputs from these pathways. We uncovered auto- and cross regulatory inputs of Hoxa1 and TALE proteins into regulation of the TALE- family of homeobox genes, suggesting mutual regulatory control of Hox proteins and genes encoding their cofactors. Finally, analysis of target genes revealed that Hoxa1 also has regulatory input into genes which control the pluripotency pathway, including core pluripotency components like *Nanog* and *Sox2*. This demonstrates a critical role for Hox proteins in controlling the balance between the pluripotential state and differentiation during neural development. This work is enhancing our understanding of the nature of evolution of the Hoxa1 gene regulatory network and its downstream target genes.