Identification of retinoic acid-responsive transcriptional regulators in human ESCs

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Abstract

Retinoic acid (RA) has been widely recognized as mediator of cell differentiation; nevertheless, under specific conditions, RA was also shown to sustain pluripotency. The effect of RA on target genes is mediated by a family of transcription factors known as nuclear receptors, including retinoic acid receptors (RARs) and retinoid acid X receptors (RXRs), which form heterodimers interacting with specific RA response elements (RAREs) located in the promoter of target genes. RAREs are classically described as direct repeats of a consensus sequence spaced by 0, 1, 2, or 5 nucleotides. This study is based on the development of a customized algorithm to discover RAREs via promoter's sequencing matching aiming to identify novel transcription factors modulated by RA, based on DRs classification, in stem cell environment. Our analysis was further implemented by a Master Regulator Analysis (MRA). Among the MR list, we selected a zinc finger (ZNF) gene whose promoter harbors both DR0, the most represented DR element in ESCs, and DR2, predominant in differentiated cells. To uncover the function of this ZNF in regulating self-renewal and early differentiation of human embryonic stem cells (hESCs) we used the loss-of-function approach based on CRISPR-Cas9 gene editing. Our preliminary data show that the loss of this specific MR gene promotes ESCs differentiation toward the neuroectodermal lineage.