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miRNA-mRNA integrative expression mapping during mouse embryonic stem cell to Neuron progenitor differentiation

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Abstract

Genome-wide transcriptome profiling of mammalian cells has given more insight into complexity of RNA world. Vast majority of RNAs are falling under non-coding category, among which ~22 nucleotides RNA is known as microRNA. It regulates gene expression by repressing translationally or cleaving mRNAs. 6-8 nucleotides region at 5' end of miRNAs bind to 3' UTR region of mRNA called 'seed region'. This binding is either completely or incompletely complementary. Complete complementarity associates with RNA Induced Silencing Complex (RISC) that able to degrade mRNA with the help of Argonaute protein (Ago). But, incomplete complementarity is believed to be in a type of poised state that can be removed during requirement of that particular protein synthesis. mRNA translational repression by miRNA leads to subsequent mRNA destabilization. These dynamics of miRNA and mRNA integrative expression was further studied in embryonic stem cell to Neuron Progenitor differentiation system. Upon retinoic acid treatment to mouse embryonic stem cell line (R1), without LIF and 2i inhibitors that maintain undifferentiating state in ESC, cells were differentiated to neuronal cell lineage. To study, the dynamic changes in expression during differentiation we performed both microRNA and mRNA sequencing separately in these two states with biologically duplicated samples. Interestingly, we came up with 82 differentially regulated miRNAs, 9 lncRNAs and 4336 mRNA genes during this phase. Along with these 31 novel miRNAs were identified, among them 17 were identified that specific to ESC and 14 were in NP. Interaction maps of miRNA-mRNA was confirmed the down regulation of targeted mRNAs due to upregulated miRNAs during differentiation. KEGG pathways analysis of these genes showed downregulation of signaling pathways regulating pluripotency of stem cells (by miR-466m-3p, miR-466k, miR-1198 and miR344e) and upregulation of axon guidance and Neurotrophin signaling pathways that involves in differentiation of neuronal cells. These studies reveal genome wide miRNAs and mRNAs interaction map in ESC to NP differentiation. That will help in understanding of controlled gene expression patterns during neuronal differentiation due to miRNAs and lncRNAs parallel expressions.

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