Non-coding RNAs putatively acting as ceRNAs in embryonic stem cells

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The cells composing the human body share the same genetic code, but their different transcriptomes, controlled by a complex gene expression regulation system, enable the existence of several different cell types. Recently, a new regulatory mechanism based in the idea that different RNAs can compete for miRNAs ligation was proposed. Named as competing endogenous RNAs (ceRNAs), those molecules share miRNAs response elements with other co-expressed RNAs, acting as miRNAs sponges and leaving the mRNAs targets free to be translated. This competition mechanism is present in several cells, but it has been poorly investigated in embryonic stem cells (ESCs). The aim of this study was search for non-coding RNAs which may act as ceRNAs in ESCs and may be involved in stem state maintenance. For this purpose, RNA-seq data from ESCs and differentiated cells (DIFCs) was downloaded from GEO (GSE64417). The reads were aligned using STAR and differentially expressed mRNAs, lncRNAs, pseudogenes and miRNAs were detected using the package DESeq2. Pearson correlation (PeC) between mRNAs and lncRNAs or pseudogenes and partial correlation (PaC) between mRNAs and ncRNAS controlling for 5 transcription factors (TFs) were estimated using the R packages Hmisc and ggm, respectively. TFs binding the studied genes were retrieved from JASPAR database and gene ontology analysis was performed using the package GOseq. From ESCs upregulated genes ($log2FC \geq 1$; $padj < 0.05$), those targeted by ESCs upregulated miRNAs were considered for ceRNA searching. Pairs of mRNAs and lncRNAs or pseudogenes targeted by the same miRNAs and whose PeC was $r \geq 0.6$ ($p < 0.05$) were selected. Positive correlation due to shared regulatory genomic sequences was discarded since the pairs RNAs are coded in different chromosomes. PaC r values pointed that TFs have no influence over the correlations observed. Moreover, pairs observed as positively correlated in DIFCs were removed from the analysis. This filtering process ended up with 107 mRNA-ncRNA pairs. An onthology analysis revealed three mRNAs involved in stem cell population maintenance: FGF2, FZD7 and SALL4. FGF2 is targeted by 3 miRNAs which are putatively sponged by GAS5, POU5F1P3, RP11-L69L16.5 and LINC001194. The following steps are find other pairs putatively important to the ESCs maintenance and include circRNAs in the list of ceRNAs acting in these cells.

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