Long Noncoding RNAs in Patients with Dengue: Insights into Gene Regulation

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Clinical manifestations of dengue viral infections may vary from fever to the potentially deadly dengue hemorrhagic fever and dengue shock syndrome. Several studies have been published investigating global gene expression changes between healthy subjects and dengue-infected patients with different clinical manifestations. However, none of these studies have analyzed the putative role of long noncoding RNAs (lncRNAs) during these conditions. Here, we performed a meta-analysis using three publicly available microarray datasets of dengue-infected patients, focusing on lncRNA expression and their potential mechanisms in gene regulation. In order to identify probes that represent lncRNAs, we have reannotated all major commercial microarray platforms. The reannotation consisted in cross-referencing the genomic coordinates of microarray probe sequences to the gene sequences of the following databases: Gencode, Noncode, LNCipedia and MiTranscriptome. By doing this, we identified 6603 probes that represent potential lncRNAs. We then re-analyzed three studies from the Gene Expression Omnibus database (GSE18090, GSE43777 and GSE51808) composed of 60 control samples, 66 uncomplicated dengue patients and 60 severe dengue patients in total. Differential expression analyses using LIMMA package revealed that the expression of hundreds of transcripts were consistently altered between patients infected with dengue and healthy subjects in the three studies (p-value < 0.005 and absolute log2 of fold-change > 0.32). Of those, 12 were annotated as lncRNAs. One long noncoding RNA with lower expression in Dengue is TUG1, which was previously described as an important gene in different types of cancer. TUG1 can bind to Polycomb Repressive Complex 2, which is known to lead to chromatin remodulation. Evidence of cis-regulation was found through the calculation of Spearman correlation coefficient between the expression of antisense lncRNAs and their sense protein-coding transcripts. This "guilty-by-association" approach suggests that, during Dengue infection, the USP30-AS1 lncRNA can modulate the alternative splicing of USP30 gene, which in turn is important for mitochondrial deubiquitination and there are several studies showing the importance of ubiquitination system in viral infections. Taken together, our analyses revealed that lncRNAs can play an important role in the immune responses to dengue infection.Financial Support: CAPES.