Identification of differentially expressed lncRNAs in metformin resistant SH-SY5Y neuroblastoma cells

Only 1.2% of the total human DNA codes for proteins, with the rest only being transcribed into regulatory RNA, known as non-coding RNA. Long non-coding RNAs (lncRNAs) are non-coding RNAs that have no or limited protein-coding potential, are >200nt in length and include- among other categories- long/large intergenic/intervening RNAs (lincRNAs), intronic lncRNAs, natural antisense transcripts (NATs) and pseudogenes. lncRNAs are key regulators of several cellular processes and have been associated with a variety of diseases, including cancer. Metformin (N,N-dimethylbiguanide) is an oral biguanide already in clinical use against diabetes, and has also been suggested to decrease incidence of various cancers, including neuroblastoma, the most common extracranial paediatric cancer arising at the sympathetic nervous system.

The present study aimed at assessing the differential expression of protein coding and, primarily, non-protein-coding RNAs between control untreated SH-SY5Y neuroblastoma cells and cells resistant to 3mM Metformin via a paired-end RNA sequencing approach.

In the first data set (untreated cells compared to cells resistant to 3mM Metformin), out of 13741 genes measured, 7855 genes were found to be differentially expressed with 108 of them falling within the lncRNA category. Among these 33 comprise lincRNAs, 24 are NATs and 18 pseudogenes. In the second data set (untreated cells compared to cells treated with 20mM Metformin) 13481 genes were tested, of which 5652 showed perturbed expression. Among them, 86 belong to the lncRNA category, and in particular 33 are lincRNAs, 19 are NATs and 13 are pseudogenes. Interestingly, 34 of the assessed lncRNAs display differential expression in both data sets. The results were obtained using a threshold of 0.05 for statistical significance (p-value) and a log fold change of expression with absolute value of at least 0.6.

Neuroblastoma cells' response to Metformin, as well as the acquisition of resistance to the drug, trigger the differential expression of a great diversity of lncRNAs. Given that Metformin is an appealing and promising therapeutic approach against neuroblastoma, these lncRNAs could in turn be used as molecular biomarkers towards better prediction, prognosis and diagnosis of the disease. Moreover, such an approach would be of interest as part of a combination therapy.