Genome-wide Search For Splicing Defects Associated with Amyotrophic Lateral Sclerosis (ALS)

Lenzken SC[(1)], Vivarelli S[(1)], Zolezzi F[(2)], Cordero F[(3)], Della Beffa C[(3)], Calogero RA[(3)] and Barabino S[(1)]

[(1)]Dipartimento di Biotecnologie e Bioscienze, Università di Milano – Bicocca, Piazza della Scienza 2-4, Milano, I 20126
[(2)]Genopolis Consortium, Università di Milano – Bicocca, Piazza della Scienza 2-4, Milano, I 20126
[(3)]Dipartimento di Scienze Cliniche e Biologiche, Università di Torino, Regione Gonzole 10, Orbassano (TO) I 10043

Motivation

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease caused by the degeneration of motor neurons. Although the cause of ALS is unknown, mutations in the gene that produces the SOD1 enzyme are associated with some cases of familial ALS. SOD1 is a powerful antioxidant that protects the body from damage caused by superoxide, a toxic free radical. It has been proposed that defects in splicing of some mRNAs, induced by oxidative stress, can play a role in ALS pathogenesis. Alterations of splicing patterns have also been observed in ALS patients and in ALS murine models, suggesting that alterations in the splicing events can contribute to ALS progression.

Methods

Using Exon 1.0 ST GeneChips, which allow the definition of alternative splicing events (ASEs) , the SH-SY5Y neuroblastoma cell line has been profiled after treatment with paraquat, which by inducing oxidative stress alters the patterns of alternative splicing. Furthermore, the same cell line stably transfected with wt and ALS mutant SOD has also been profiled.

Results

The integration of the two ALS models efficiently moderates ASE false discovery rate, one of the most critical issues in high-throughput ASEs detection. This approach allowed the identification of a total of 14 splicing events affecting respectively both internal coding exons and 5’ UTR of known gene isoforms.

Contact : raffaele.calogero@unito.it