Proceedings of the Joint Meeting AGI-SIBV-SIGA
Assisi, Italy – 19/22 September, 2011
ISBN **978-88-904570-2-9**

Oral Communication Abstract – 1.01

REPETITIVE ELEMENTS TRANSCRIPTION AND MOBILIZATION CONTRIBUTE TO HUMAN SKELETAL MUSCLE DIFFERENTIATION AND DUCHENNE MUSCULAR DYSTROPHY PROGRESSION

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Noncoding RNAs (ncRNAs) are recently considered component of chromatin, having a critical role in organizing the epigenome architecture and epigenetic memory. Genome-wide studies have revealed that ncRNAs transcription, mostly originating within intergenic regions of the genome, is far more ubiquitous than previously thought. A large part of thee transcripts originate from repetitive sequences. To this, we recently reported the first complete transcriptome produced by repetitive elements in the mammalian genome (Faulkner et al, Nat Genet 2009), which covers about 20% of overall transcripts in a cell. This study revealed that repetitive element expression is regulated in a tissue specific manner and that their expression is positively correlated with expression of neighboring genes. Notably, LINE signal dependent expression appears to be linked to their genomic redistribution, as recent reports showed de novo LINE-1 (L1) retrotransposition events in somatic as well as cancer cells (Coufal et al., Nat 2009; Huang et al., Beck et al, Iskow et al. Cell 2010). It as also been shown that L1 retrotransposition can be controlled in a tissue-specific manner and that disease-related genetic mutations can influence the frequency of L1 retrotransposition (Muotri et al Nat 2010). These findings suggest a potential role of mobile elements as mediators of somatic variations, which in turn can influence the genome and the epigenome plasticity in order to accomplish developmental programs.

The role of noncoding transcriptome in skeletal muscle cell differentiation is unexplored and it may represent an opportunity to unravel and characterize its contribution to dystrophic muscle degeneration.

To this we generated deepseq transcriptome CAGE libraries from three Duchenne Muscular Dystrophy (DMD) patients and three controls' primary myoblasts. Cytosolic and nuclear RNA fractions were collected and deep-sequenced at different time points: proliferating myoblasts, myotubes upon differentiation induction (day 1 of differentiation) and differentiated myotubes (day 8 of differentiation). This analysis highlighted that LINEs constitute the bulk of repetitive element transcription and that the resulting RNAs are selectively localized in the nucleus. Notably the largest difference between DMD and control samples appears to be in nuclear transcriptome of all repetitive elements including LINE-1. Further, by using a Taqman-based approach, we analysed L1 copy number variation in proliferating and differentiating myoblasts derived from the same DMD patients and healthy donors; surprisingly, new retrotrasposition events occured during control's differentiation and not during DMD's differentiation and profound differences are featured between patients compared to control.

Data will be presented showing a direct link between L1 transcription, myogenic program and its alteration in DMD progression.