A COMBINATION OF BOTH PROTEOMIC AND GENETIC APPROACHES TO IDENTIFY DE-REGULATED PATHWAYS IN PROGERIA, AN ACCELERATED AGING DISORDER.

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A point mutation in LMNA gene, codifying for nuclear Lamin A, is responsible for Hutchinson-Guilford Progeria Syndrome or Progeria, an accelerated aging disorder in which most of the features of normal aging are present at very early ages. Furthermore, cell lines carrying the mutation become senescent at early passages, suggesting a link between aging at cellular and organism level. We used both proteomic and genetic approaches to identify altered pathways in cell lines carrying the mutation as well as in Mesenchymal Stem Cells over-expressing the truncated isoform of the protein. First we design an *in vivo* metabolic labelling experiment -SILAC- with the aim of detecting proteins modulated in a Progeria-derived fibroblast cell line compared to a normal fibroblast cell line. Quantitative results show major changes in cellular processes as important as Protein Synthesis, Differentiation, Metabolism and Cytoskeleton arrangement. Secondly, in order to investigate the effect of the Lamin A mutation in the regenerative potential of the Mesenchymal Stem Cells we used a lentiviral system to transduce Human Umbilical Cord Mesenchymal Stem Cells with both wt Lamin A and the mutated form -progerin-. The differentiation study of the transduced cells suggests changes in their osteogenic and adipogenic potential and a de-regulation of β-catenin pathway, indicating that tissue regeneration is also altered in Progeria-affected individuals. Globally, our results will help to understand not only the accelerated aging process, but also the cellular senescence and the normal aging as well.