Translational proteomic and metabolomic investigations to assess gene therapy/delivery efficacy in rare genetic disease

ShT-01.3-2

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Ataxia Telangiectasia (A-T) is a rare neurodegenerative disease caused by biallelic mutations in the Ataxia Telangiectasia Mutated gene (ATM). No cure is currently available for these patients apart the positive effects on neurologic features of A-T patients by dexamethasone administration through autologous erythrocytes. We recently developed a lentiviral system to deliver shorter but functional ATM variants, capable to restore some impaired biological processes of A-T cells. Here we performed proteomic and metabolomic analyses of an A-T cellular model, treated with two different ATM variants and compared to WT cells. We could demonstrate that omics sciences are suitable tools in choosing the most performant gene variant to be administered in a target cell line. By High specificity pruning statistic of proteomic data, we found out that A-T cells exhibit a) impaired RNA splicing, b) weakened protein folding, c) constitutive inflammation, d) impaired extracellular matrix organization. Alternative biological assays confirmed the observed deficiencies. Moreover, matched proteomic and metabolomic analyses revealed that glycolysis, mitochondrial metabolism, redox homeostasis are impaired in A-T, also proven by alternative biochemical techniques. The same omics approaches achieved on treated A-T cells (by lentiviral transduction of ATM SINT and ATM 4-53, two shorter ATM variants) reveled that ATM SINT is the finest ATM variant to be administered for recovering the altered A-T phenotype, making the protein and metabolite levels similar to WT ones. Also, biochemical functional tests of administered ATM variants confirmed the observed restoration process.
In conclusion, multi-omics approach represents a suitable tool in choosing the best biological therapy to be administered to achieve gene therapy or gene delivery strategy.

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