OFFICIAL ABSTRACT and CERTIFICATION

The Effect of P57KIP2 Down-Regulation via Lentiviral shRNA Knockdown of CDKN1C on the Glucocorticoid Dexamthasone's Function in Culture Peripheral-Blood Derived CD34+ Cells

Jonah Thomas
Northport High School, Northport, NY, USA

In certain cases of Diamond-Blackfan Anemia (DBA) erythroid cells are resistant to the effects of glucocorticoids. Glucocorticoids are believed to upregulate a Cyclin Dependant Kinase Inhibator, P57KIP2, however it's effects on healthy blood cells have not been tested in humans. This experiment tests the effects of the glucocorticoid Dexamethasone on cell proliferation rates and differentiation. It does so under the conditions of P57KIP2 knockdown. Lentiviruses are synthesized for P57KIP2 gene CDKN1C knockdown and Luciferase transduction control. Effective transduction was tested using western blot. A cell proliferation assay was conducted to test cell proliferation rates and flow cytometry was used to measure cellular differentiation. Results indicated significant increase in cell proliferation rates when treated with Dexamethasone in control knockdown groups, and demonstrated minimal effects in P57KIP2 knockdown groups. In addition, the luciferase control group experienced a significant decrease in differentiation when treated with Dexamethasone. However, the difference in differentiation in P57KIP2 knockdown groups was less significant. These experiments demonstrate that glucocorticoid resistance in DBA cells are potentially due to a problem in the P57KIP2 pathway. This study serves as justification for future studies on the P57KIP2 pathway in DBA cells. This study serves as a preliminary study in understanding the mechanisms of resistance in DBA cells. If this pathway is explored, a solution for many DBA patients can be developed. DBA is a disease with a low patient population and minimal main stream attention. My goal in sharing this research was to raise awareness for this rare disease.

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