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Basic Science

Abstract Title
Atm restoration prevents cancer and ataxia outcomes in neuropediatric disorder, ataxia telangiectasia.

Background
Ataxia Telangiectasia (AT) is an autosomal recessive neuropediatric disorder caused by a deficiency in the AT Mutated (ATM) protein. AT is marked by progressive motor dysfunction, usually putting kids in a wheelchair by age 10, immune deficiency, and cancer predisposition. We have developed a novel Atm-deficient mouse model with a clinically relevant nonsense mutation in the Atm gene, and notably, the first model to exhibit the ataxia phenotype. Using this model, we tested novel small molecule read-through (SMRT) compounds, which were shown to restore low levels of Atm production and offer therapeutic benefits. However, before clinical trials, the direct mechanism of Atm restoration behind the therapeutic effect needs to be confirmed.

Objective
In this study we aim to show that restoring even low levels of ATM production in cells systemwide will improve the quality and duration of AT patient's lives.

Methods
We will generate an inducible murine expression model of AT. The model is created by adding an estrogen receptor 2 ligand-binding domain (ERT2-LBD) upstream of the Atm gene such that Atm translocation into the nucleus will be tamoxifen-inducible. The mouse genome is edited using an Easi-CRISPR strategy with ssDNA as a template. Successful integration of the inducible system will be validated using H2AX phosphorylation as an indicator of an active Atm pathway. This model will then help us determine whether restoration of even low levels of Atm protein directly has therapeutic effects on the cancer and immune deficiency phenotype. Our collaborators will also use the mouse model to study the effects of Atm restoration on ataxia.

Results
ssDNA template was successfully created and microinjections done for creation of mouse model.

Conclusion
This model represents the final pre-clinical step before SMRT compounds can enter clinical trials. Further applications of this model include identifying leukemic and restorative determinants of microRNA regulation in the Atm-signaling pathway.

Authors

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