Optimizing a High Throughput Screen for Testing Therapeutics in a Novel Mouse Model of Ataxia Telangiectasia

Xie, Christine (School: Palos Verdes High School)

Ataxia Telangiectasia (A-T) is a rare (one in ~100,000) autosomal recessive neurogenetic disorder, primarily characterized by cerebellar atrophy and progressive severe motor coordination loss. A-T patients become confined to wheelchairs by their early teens and die at a median age of 16 years old. Currently, no cure exists, and care is palliative. A-T is caused by a deficiency in the A-T Mutated (ATM) protein as the result of genetic mutations that prevent protein translation. Therapeutics capable of restoring ATM are in development, necessitating preclinical in vitro assays for evaluating their effectiveness. Thus, the proposed objective is to create a high throughput cell-based assay with which to quantitatively measure the ability of therapeutics to restore ATM. To develop this assay, ATM-rich splenocytes from a recently developed A-T mouse model were evaluated for feasibility as an in vitro testing vehicle. Then, an ATM detection assay was optimized to accurately and precisely measure ATM in splenocytes that exhibit normal levels of ATM and those that are ATM-deficient. It was found that these splenocytes are highly promising for quantitatively measuring ATM protein, with maximal survivability and viability occurring 48 hours after thawing. Furthermore, it was determined that a ~4.0 µg/10 µL splenocyte dilution with a 1 hour incubation period is optimal for the assay. Therefore, this in vitro model and optimized high throughput screen provides a crucial foundation for continuing investigation on the potency and efficacy of various therapeutics on restoration of ATM protein in a clinically relevant set of cells.

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