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Targeting neural stem cells in situ to correct the neurological disorders in Atm-null mice

Paul K. Wong
UT MD Anderson Cancer Center, USA

Ataxia-telangiectasia (A-T) is a genetic disease with multiple syndromes, the most prominent of which is neurodegeneration. When activated by stress, ATM regulates complex down-stream pathways in the cell's defense network. Without ATM, reactive oxygen species (ROS) build up over time resulting in progressive neurodegeneration. In A-T brain, the subventricular zone neural stem cells (NSCs) and the cerebellum Purkinje cells are severely affected. Exhaustion of NSCs compensatory mechanism leads to symptomatic disease progression. We are interested in combinational therapeutic approaches that restore the redox balance in the ATM-deficient cells by redox buffering agents while simultaneously correcting the defective NSCs so that they can perform their neuronal regenerative task.

We have identified a specific ROS-p38-Bmi1-p21 signaling pathway as a possible underlying mechanism causing defects of ATM-deficient NSCs. Significantly, treatment of the *Atm*-null mice with the a p38-inhibitor restores the dysregulated signaling in NSCs and corrects the neurologic deficits in the $Atm^{-/-}$ mice. Furthermore, using a potent antioxidant monosodium luminol to target the upstream effects of ROS, we are also able to restore the motor coordination deficits of the $Atm^{-/-}$ mice. Together, these findings may offer some hope in A-T therapy because we are able to slow down the degenerative processes and rescue the neurons from demise when we observe the first clinical signs of motor coordination deficits. This provides a promising approach to replace degenerated neurons for A-T by targeting dysfunctional NSCs in situ rather than transplantation of stem cells. This resident-stem-cell-based therapy could also be beneficial to other neurodegenerative diseases

Biography

Paul Wong, Ph.D., studies the mechanisms of retroviral-induced and defective gene-mediated neurodegeneration and cancer. A major recent breakthrough in his research involves studies on the genetic disease ataxia telangiectasia (A-T). A prominent feature of A-T is the loss of cerebellum Purkinje cells resulting in in-coordination. Using a mouse model, his lab shows that loss of ATM impairs self-renewal of NSCs that renders them unable to regenerate to replace the lost neurons. Treatment targeting the dysregulated NSCs restores and corrects the motor deficits in the A-T mice. This provides a promising approach to replace degenerated neurons for A-T by targeting NSCs *in situ* rather than transplantation of stem cells

pkwong@mdanderson.org