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Selected Publication

Li J et al (2012) Nuclear accumulation of HDAC4 in ATM deficiency promotes neurodegeneration in ataxia telangiectasia. *Nature Medicine*, doi:10.1038/nm.2709

Research Aims and Interests

Cancer Biology & Aging – The unexpected role of the ATM protein in late-life dementia

Ataxia telangiectasia is a genetic deficiency of the ATM protein that leads to an childhood syndrome of abnormalities the most prominent of which are movement disorders associated with a massive degeneration of neurons in cerebellar cortex. lzheimer's disease is a sporadic late life dementing illness of unknown etiology. Symptoms include neurological abnormalities that include disorders of memory and executive functioning, accompanied by a massive degeneration of the neurons in hippocampus and several subcortical structures. These two diseases are separated by seven decades of life and by regions of cell loss. Yet in both diseases the loss of neurons is preceded by ectopic cell cycle activity in the populations at risk. As ATM is expressed throughout the lifespan, we asked whether a loss of ATM activity might perhaps be a factor in the death of neurons in Alzheimer's disease. We used four separate ATM-dependent markers – nuclear translocation of HDAC4, trimethylation of histone H3, loss of DNA hydroxymethylation and neuronal cell cycle activity – to identify neurons in which ATM activity was lost. We found that in regions of the Alzheimer's brain where degeneration is prevalent, neuronal ATM activity fails. Judged either by neuropathology or by clinical severity, ATM activity in the affected regions was negatively correlated with disease stage. Significantly, we found a high degree of co-occurrence of the markers in individual neurons. Our findings support a model in which, on a neuron-by-neuron basis, there is a concerted failure of multiple ATM-dependent processes as Alzheimer's advances. Our data identify a previously unknown role for the ATM kinase in Alzheimer's pathogenesis and suggest that therapies aimed at maintaining ATM activity may have promise as strategies for slowing or preventing Alzheimer's disease.