Neuroinflammation Contributes to the Neuronal Phenotype in Ataxia-telangiectasia: A Rat Model of Ataxia-telangiectasia

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Ataxia-telangiectasia (A-T), an autosomal recessive disease caused by mutations in the *ATM* gene is characterised by cerebellar atrophy and progressive neurodegeneration which has been poorly recapitulated in *Atm* mutant mice. Consequently, pathways leading to neurodegeneration in A-T are poorly understood. We describe here the generation of an *Atm* knockout rat model that does not display cerebellar atrophy but instead paralysis and spinal cord atrophy, reminiscent of that seen in milder forms of the disorder in A-T patients. Loss of Atm in neurons leads to accumulation of cytosolic DNA, increased cytokine production and constitutive activation of microglia consistent with a neuroinflammatory phenotype. Rats lacking ATM had significant loss of motor neurons and microgliosis in the spinal cord, consistent with onset of paralysis. Since short term treatment with steroids has been shown to improve the neurological signs in A-T patients we determined whether that might also be the case for Atm-deficient rats. Betamethasone treatment extended the lifespan of *Atm* knockout rats, prevented microglial activation and significantly decreased neuroinflammatory changes and motor neuron loss. These results point to unrepaired damage to DNA leading to significant levels of cytosolic DNA in Atm -deficient neurons and microglia and as a consequence activation of the cGAS-STING pathway and cytokine production.This in turn would increase the inflammatory microenvironment leading to dysfunction and death of neurons. Thus the rat model represents a suitable one for studying neurodegeneration in A-T and adds support for the use of anti-inflammatory drugs for the treatment of neurodegeneration in A-T patients.