

Rats with a missense mutation in *Atm* display neuroinflammation and neurodegeneration subsequent to accumulation of cytosolic DNA following unrepaired DNA damage

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Abstract

Mutations in the ataxia - telangiectasia (A - T) - mutated (*ATM*) gene give rise to the human genetic disorder A - T, characterized by immunodeficiency, cancer predisposition, and neurodegeneration. Whereas a series of animal models recapitulate much of the A - T phenotype, they fail to present with ataxia or neurodegeneration. We describe here the generation of an *Atm* missense mutant [amino acid change of leucine (L) to proline (P) at position 2262 (L2262P)] rat by intracytoplasmic injection (ICSI) of mutant sperm into oocytes. *Atm* - mutant rats (*Atm*^{L2262P/L2262P}) expressed low levels of ATM protein, suggesting a destabilizing effect of the mutation, and had a significantly reduced lifespan compared with *Atm*^{+/+}. Whereas these rats did not show cerebellar atrophy, they succumbed to hind - limb paralysis (45%), and the remainder developed tumors. Closer examination revealed the presence of both dsDNA and ssDNA in the cytoplasm of cells in the hippocampus, cerebellum, and spinal cord of *Atm*^{L2262P/L2262P} rats. Significantly increased levels of IFN - β and IL - 1 β in all 3 tissues were indicative of DNA damage induction of the type 1 IFN response. This was further supported by NF - κ B activation, as evidenced by p65 phosphorylation (P65) and translocation to the nucleus in the spinal cord and parahippocampus. Other evidence of neuroinflammation in the brain and spinal cord was the loss of motor neurons and the presence of increased activation of microglia. These data provide support for a proinflammatory phenotype that is manifested in the *Atm* mutant rat as hind - limb paralysis. This mutant represents a useful model to investigate the importance of neuroinflammation in A - T.

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