Signalling of DNA single strand breaks and links to neurodegeneration.

https://neurodegenerationresearch.eu/survey/signalling-of-dna-single-strand-breaks-and-links-to-neurodegeneration/

Name of Fellow

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Funder

Wellcome Trust

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Signalling of DNA single strand breaks and links to neurodegeneration.

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The project/programme is most relevant to:

Neurodegenerative disease in general

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Research Abstract

ATM protein kinase is mutated in individuals with the rare genetic disorder Ataxia Telangiectasia

(A-T), characterised by progressive neurodegeneration, genomic instability and immunodeficiency. ATMs primary function involves its activation by DNA double-strand breaks (DSBs), resulting in the phosphorylation of over a thousand vital cellular substrates. However, exciting new observations revealed that ATM activity is stimulated by DNA single-strand breaks (SSBs), which arise from the intrinsic c hemical instability of DNA. SSB-dependent ATM activation prevents the replication of damaged DNA and accrual of deleterious DSBs. Since these results challenge our perception of the role of ATM in genome stability, which focuses on the role of ATM in DSB repair, it will be critical to define the molecular mechanism of ATM activation by SSBs. Progressive neurological disorders, like A-T, are often linked with defective DNA repair and signalling. It is, however, unlikely that compromised DSB sign alling or impaired checkpoint control following SSBs underpins the neurological phenotype of A-T. Importantly, we have discovered that ATM deficiency down-regulates XRCC1, a scaffold protein essential for endogenous DNA damage repair. These important observations lead to new questions relating to the mechanism by which ATM controls XRCC1, and how this contributes to the neurological pathology of A-T.

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Fellowships

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