Inhibiting the DNA damage response pathway promotes functional recovery after spinal cord injury

Ahmed, Zubair; Tuxworth, Richard

DOI:
10.1002/ctd2.106

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Ahmed, Z & Tuxworth, R 2022, 'Inhibiting the DNA damage response pathway promotes functional recovery after spinal cord injury', *Clinical and Translational Discovery*, vol. 2, no. 3, e106. https://doi.org/10.1002/ctd2.106

Received: 23 June 2022 | Accepted: 23 June 2022

DOI: 10.1002/ctd2.106

CLINICAL AND TRANSLATIONAL DISCOVERY Open Access WILEY

COMMENTARY

Inhibiting the DNA damage response pathway promotes functional recovery after spinal cord injury

Zubair Ahmed[1,2] | **Richard I. Tuxworth**[3]

[1]Neuroscience and Ophthalmology, Institute of Inflammation and Ageing, University of Birmingham, Edgbaston, UK

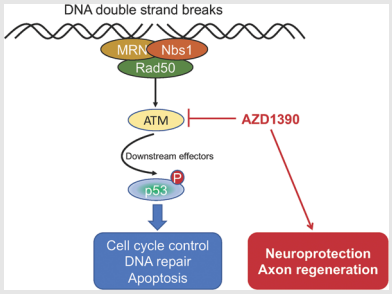
[2]Centre for Trauma Sciences Research, University of Birmingham, Edgbaston, UK

[3]Birmingham Center for Genome Biology, Institute of Cancer and Genomic Sciences, University of Birmingham, Edgbaston, UK

Correspondence
Zubair Ahmed, Neuroscience and Ophthalmology, Institute of Inflammation and Ageing, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK.
Email: z.ahmed.1@bham.ac.uk

Richard I. Tuxworth, Birmingham Center for Genome Biology, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, B15 2TT, UK.
Email: r.i.tuxworth@bham.ac.uk

Graphical Abstract



Ahmed and Tuxworth show that inhibiting the DNA damage response pathway using a small molecule inhibitor of ATM, AZD1390, promotes axon regeneration and functional recovery after spinal cord injury. AZD1390 is orally bioavailable and reaches the central nervous system in sufficient amounts to engage the target protein and hence represents an easy-to-deliver compound to promote recovery of function in spinal cord injured patients.

Received: 23 June 2022 | Accepted: 23 June 2022

DOI: 10.1002/ctd2.106

CLINICAL AND TRANSLATIONAL DISCOVERY Open Access WILEY

COMMENTARY

Inhibiting the DNA damage response pathway promotes functional recovery after spinal cord injury

Zubair Ahmed[1,2] | **Richard I. Tuxworth**[3]

[1]Neuroscience and Ophthalmology, Institute of Inflammation and Ageing, University of Birmingham, Edgbaston, UK

[2]Centre for Trauma Sciences Research, University of Birmingham, Edgbaston, UK

[3]Birmingham Center for Genome Biology, Institute of Cancer and Genomic Sciences, University of Birmingham, Edgbaston, UK

Correspondence
Zubair Ahmed, Neuroscience and Ophthalmology, Institute of Inflammation and Ageing, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK.
Email: z.ahmed.1@bham.ac.uk

Richard I. Tuxworth, Birmingham Center for Genome Biology, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, B15 2TT, UK.
Email: r.i.tuxworth@bham.ac.uk

Funding information
Medical Research Council, Grant/Award Number: MC_PC_15048

Abstract

Spinal cord injury (SCI) affects up to 1.26 million people every year, leading to permanent disability and death. The biggest causes of SCI are motor vehicle accidents, falls and interpersonal violence with clinical outcomes very much dependent on the severity and location of the lesion. Frequently, there is loss of motor or sensory function below the level of injury. At present, there are no restorative treatments for SCI patients, with only palliative treatments on offer and complicated further by the low intrinsic capacity of the central nervous system to regenerate. A recent study by Tuxworth and Ahmed, published in *Clinical and Translational Medicine*[1] shows that inhibiting ataxia-telangiectasia mutated (ATM) kinase, a central regulator of the DNA damage response pathway, promoted axon regeneration and remarkable improvements in sensory and motor function after SCI in both mice and rats. Moreover, the ATM inhibitor, AZD1390, is potent and highly selective, orally bioavailable and brain-penetrant.[2] AZD1390 is currently being developed for the treatment of brain cancers but with its simple route of administration (oral), has the potential to be re-purposed for use in SCI.

In all eukaryotic cells, DNA integrity is challenged frequently by base modifications and strand breaks. Rapid recognition and accurate repair of DNA damage are crucial to maintaining genome stability. Amongst these types of lesions, DNA double-strand breaks (DSBs) are considered the most genotoxic and can appear in response to a variety of causes such as ionizing radiation, reactive chemicals or indirectly via the processing of other types of DNA lesions or breakdown of DNA replication forks.[3] Upon detection of DSBs, cells activate the DNA damage response (DDR), a signal transduction pathway that promotes repair processes and activates DNA damage-dependent checkpoint proteins that slow or halt cell cycle progression to allow more time for DNA repair.[3] If the damage is too extensive, the DDR can trigger cell death.

DSBs are a feature of many neurodegenerative diseases, including Alzheimer's Disease, amyotrophic lateral sclerosis (ALS) and Huntington's disease. All of these diseases show dysfunction in the DDR and DSBs are linked with autophagy and apoptosis in neurodegeneration.[5] DSBs are also a feature after neurotrauma, including spinal cord injury (SCI) and stroke.[6–8] Unrepaired DSBs in neurons

lead to persistent activation of the DDR and are a potential trigger for dysregulation of the cell cycle and aberrant re-entry of neurons into the G_1-phase leading to neural dysfunction, apoptosis and senescence.[9]

DSBs are sensed by the MRN complex, which comprises Mre11, Rad50 and NBS1/Nbn. Downstream, the ataxia-telangiectasia mutated (ATM) and ATM and RAD3-related (ATR) protein kinases are central regulators of the DDR, activating multiple downstream kinases, such as checkpoint 1/2 (Chk1/2).[4] We have recently shown that the ATM pathway is activated in dorsal root ganglion neurons (DRGN) after SCI and that suppression of ATM or Mre11 upstream, using small molecule pharmacological inhibitors promotes recovery of sensory and motor function after SCI.[8] KU-60019, an ATM inhibitor, reduced γH2Ax$^+$ foci (a common way to monitor direct activation of the DDR[8]) and promoted significant functional recovery after SCI, but required twice-weekly injections, directly into the cerebrospinal fluid (CSF). Recently, however, the pharmacodynamic/ pharmacokinetic profile of a central nervous system (CNS)-penetrant, highly potent and highly selective, orally bioavailable ATM inhibitor, AZD1390, was described.[2] AZD1390 has > 10 000-fold selectively over kinases within the same family and a cell IC_{50} = 0.78 nM. Significant concentrations of AZD1390 were present in the brain after oral administration and bioavailable for at least 8 hours and in syngeneic and patient-derived brain gliomas established in mice, AZD1390 dosed in combination with daily ionizing radiation therapy-induced tumour regression and prolonged survival.[2] AZD1390 is therefore being developed as a radiosensitizer in CNS malignancies.[2]

In the Tuxworth and Ahmed study,[1] we used rodent preclinical models of SCI[10] to determine if oral delivery of AZD1390 would suppress ATM signalling after SCI without the need for delivery directly into the CNS. We first showed that AZD1390 efficiently suppressed ATM activation in cultured DRGN, promoting significant DRGN survival and neurite outgrowth. In vitro, KU-60019 also promoted similar levels of DRGN survival and neurite outgrowth as AZD1390. Oral delivery of AZD1390 and KU-60019 after SCI in mice demonstrated that only oral delivery of AZD1390 suppressed ATM activation but, in contrast, oral KU-60019 had no effect on ATM. AZD1390 also promoted significant electrophysiological, sensory and motor function recovery after SCI, and again, oral KU-60019 had no effect. These results demonstrated that sufficient amounts of AZD1390 reached the CNS after oral delivery to stimulate recovery, whilst oral KU-60019 did not reach the CNS tissues. These results demonstrate that inhibition of ATM with a brain penetrant AZD1390 might be an effective therapy to restore lost function after SCI.

In conclusion, oral AZD1390 to suppress ATM activation in DRGN after SCI has profound effects on axon regeneration and functional recovery, and represents a promising therapy for restoration of lost function for SCI patients.

ACKNOWLEDGEMENT

This research was funded by a grant from the Medical Research Council UK (grant number: MC_PC_15048).

CONFLICT OF INTEREST

Zubair Ahmed and Richard I. Tuxworth are inventors on a patent related to this work.

ORCID

Zubair Ahmed https://orcid.org/0000-0001-6267-6442

REFERENCES

1. Ahmed Z, Tuxworth RI. The brain penetrant ATM inhibitor, AZD1390, promotes axon regeneration and functional recovery in preclinical models of spinal cord injury. *Clin Transl Med*. 2022;4(6):eaat1719. doi:10.1002/ctm2.962
2. Durant ST, Zheng L, Wang Y, et al. The brain-penetrant clinical ATM inhibitor AZD1390 radiosensitizes and improves survival of preclinical brain tumor models. *Sci Adv*. 2018;4(6):eaat1719.
3. Balmus G, Pilger D, Coates J, et al. ATM orchestrates the DNA-damage response to counter toxic non-homologous end-joining at broken replication forks. *Nat Commun*. 2019;10(1):87.
4. Blackford AN, Jackson SP. ATM, ATR, and DNA-PK: the trinity at the heart of the DNA damage response. *Mol Cell*. 2017;66(6):801-817.
5. Zhu LS, Wang DQ, Cui K, Liu D, Zhu LQ. Emerging perspectives on DNA double-strand breaks in neurodegenerative diseases. *Curr Neuropharmacol*. 2019;17(12):1146-1157.
6. Kotipatruni RR, Dasari VR, Veeravalli KK, Dinh DH, Fassett D, Rao JS. p53- and Bax-mediated apoptosis in injured rat spinal cord. *Neurochem Res*. 2011;36(11):2063-2074.
7. Hayashi T, Sakurai M, Abe K, Sadahiro M, Tabayashi K, Itoyama Y. Apoptosis of motor neurons with induction of caspases in the spinal cord after ischemia. *Stroke*. 1998;29(5):1007-1012.
8. Tuxworth RI, Taylor MJ, Martin Anduaga A, et al. Attenuating the DNA damage response to double-strand breaks restores function in models of CNS neurodegeneration. *Brain Commun*. 2019;1(1):fcz005.
9. Herrup K, Neve R, Ackerman SL, Copani A. Divide and die: cell cycle events as triggers of nerve cell death. *J Neurosci*. 2004;24(42):9232-9239.
10. Surey S, Berry M, Logan A, Bicknell R, Ahmed Z. Differential cavitation, angiogenesis and wound-healing responses in injured mouse and rat spinal cords. *Neuroscience*. 2014;275:62-80.

How to cite this article: Ahmed Z, Tuxworth RI. Inhibiting the DNA damage response pathway promotes functional recovery after spinal cord injury. *Clin Transl Disc*. 2022;2:e106. https://doi.org/10.1002/ctd2.106