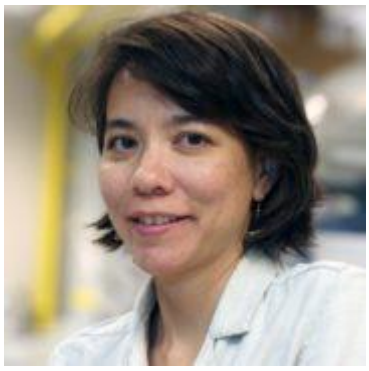
AT cerebellar neurodegeneration and inositol phosphate signalling



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LENGTH: Concluded

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This project has now completed. The proposal was based on a previous finding from the Paull laboratory that the cerebellum obtained from deceased AT individuals has reduced levels of expression of proteins that are involved in calcium signalling, which is known to be important for cerebellar function. Similar protein expression changes have been observed in other patients with progressive ataxia. One goal of this proposal was to examine whether this was also observed at the mRNA level (that is the transcript level), with mRNA being the cellular molecule used to make proteins. This would help to provide insight into the basis underlying such changes. A second goal was to examine how loss of ATM affects calcium signalling using human neurons in culture.

For the first goal, mRNA expression was examined in normal and age-matched cerebella from normal and AT individuals. In parallel, mRNA expression was also examined in the cortex, a brain region less affected in AT, to determine if the changes were cerebellum-specific. Results from this analysis showed that mRNA expression in AT individuals is very different from normal individuals, although there is significant heterogeneity among the AT individuals. The differences were most extreme in the cerebellum tissue, with fewer changes observed in the cortex. Of the mRNAs that were strongly reduced, 13 genes were known to be associated with ataxia in other familial disorders, including those involved in calcium signalling. These findings suggest that ATM loss affects gene expression in multiple pathways that are necessary for normal cerebellum function, not only calcium signalling.

To investigate the mechanisms underlying ATM loss and altered gene expression, a neuronal cell model was used. From previous work, Paull had observed that DNA damage and RNA-containing structures called called R-loops arise at sites of active transcription in the absence of ATM. In the neuronal cells, loss of ATM caused higher levels of DNA damage and higher levels of R-loops at certain sites. Interestingly, treatment with an anti-oxidant reduced the level of R-loops specifically in AT cells.

These findings demonstrate that ATM has a unique role in the cerebellum and are consistent with the notion that loss of ATM affects the expression of genes that are critical for cerebella function. They suggest that oxidative damage may have an additive impact on impairing ATM function in the cerebellum. Although further studies are required to gain insight into the precise mechanism, they suggest that agents that prevent oxidation-induced DNA damage have the potential to diminish the

impact of ATM loss. They provide important insight into the unique or special function of ATM in the cerebellum, which, if clearly understood, could help target treatment.