Decreasing Neuronal Death: Towards a Better Understanding

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Introduction

Neurones are a major site of onset for mitochondrial disease which causes neuronal death, resulting in symptoms such as seizures and strokes. [1] The mechanism behind the death of neurones is not well understood, however dysfunction of the mitochondria, found in the neurones, is thought to contribute.[2] This causes "dying back" and degeneration of the nerve. [3] If we are able to confirm that improving the action of mitochondria will decrease the extent of the neuropathy, we may be able to eventually prevent neurodegeneration associated with mitochondrial disease.

Aims

To examine whether known mitochondria-improving compounds will decrease the extent of neuropathy in both a wild type cell line and a mutant cell line with mitochondrial dysfunction.

Methods

- Induced pluripotent stem cells were cultured and differentiated into induced Ngn2 neurones.
- The neurones were given a dose of Bezafibrate which is a mitochondrial-improving compound.
- The neurones were then dosed with a gradient of concentrations of the chemotherapy compound Paclitaxel to mimic neurone death.
- Images of the neurones were taken after incubation with the compounds.

Results

No Dose Controls

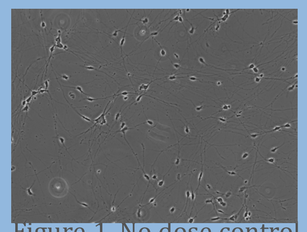

Figure 1. No dose control of the mitochondrial mutation cell line.

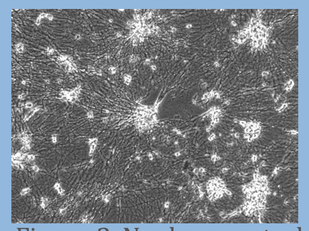

Figure 2. No dose control of the wild type cell line.

Treated with Paclitaxel

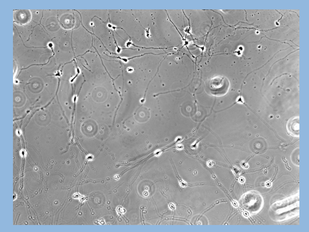

Figure 3. Mutated cell line treated with Paclitaxel to cause neuronal death.

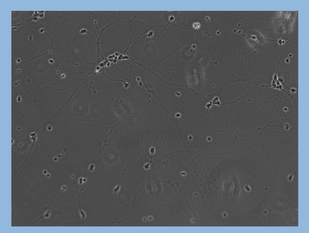

Figure 4. Wild type cell line treated with Paclitaxel to cause neuronal death.

Treated with Bezafibrate and Paclitaxel

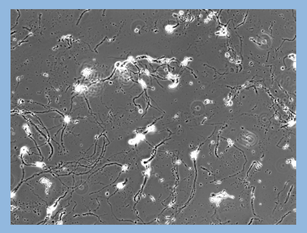

Figure 5. Mutated cell line treated first with Bezafibrate and then Paclitaxel.

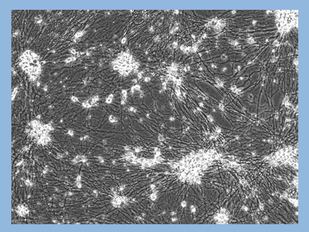

Figure 6. Wild type cell line treated firs with Bezafibrate and then Paclitaxel.

Discussion

No Dose Controls

Figures 1. and 2. show that neurones with mitochondrial dysfunction are significantly more damaged than the 'normal' neurones without having any compounds added.

Treated with Paclitaxel

Figure 4. shows that treatment with the chemotherapy compound Paclitaxel causes damage to the neurones in the wild type cell line although it does not seem to affect the already damaged mutated cell line (see Figure 3.).

Treated with Bezafibrate and Paclitaxel

When treated with Bezafibrate, the wild type cell line (Figure 6.) seems to return to the quality of the No Dose Control, while the mutated cell line neurones (Figure 5.) appear to become drastically better than in the No Dose Control (Figure 1.). More research needs to be conducted to confirm these results.

Conclusion

Bezafibrate decreases neuronal death in both wild type and mutated cell lines and can potentially reverse the effects of neuronal damage caused by mitochondrial dysfunction.

Acknowledgements

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References

1. Lax N. and Jaros E. (2011) "Neurodegeneration in Primary Mitochondrial Disorders" **In**: Reeve A. *et* al. (2012) *Mitochondrial Dysfunction in Neurodegenerative Disorders.* London: Springer-Verlag.
2. Kroemer G., Dallaporta B., Resche-Rigon M. (1998) "The mitochondrial death/life regulator in apoptosis and necrosis." *Annual Review of Physiology,* **60**: 619–642.
3. Lingor P., Koch J.C., Tonges L., Bahr M. (2012) "Axonal degeneration as a therapeutic target in the CNS." *Cell and Tissue Research,* **349**(1): 289-311