Changes in White Matter in Down Syndrome: Causes and Consequences

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Summary:

White matter is composed of nerve fibers covered by a specialized cell membrane called myelin that is produced by cells called oligodendrocytes. The myelin acts as an electrical insulator and speeds communication between neurons. Several changes in white matter have been described in people with Down syndrome including delayed onset and decreased density of the myelin. These changes are thought to contribute to the intellectual disability in Down syndrome. To understand the cause of the decrease in white matter, oligodendrocytes were made from induced pluripotent stem cells derived from people with Down syndrome. It appears that a maturation deficit in the oligodendrocytes may be driving the decreased myelin formation.

Introduction:

Down syndrome is caused by triplication of chromosome 21 and results in a well described intellectual disability. Over the years, there has been a lot of research to characterize and understand the changes in brain structure and function that cause the intellectual disability. It is thought that if the changes were understood, it could be possible to develop treatments that would increase the independence and quality of life of people with Down syndrome. Many of the studies have focused on understanding the changes in gray matter in the brain – i.e. changes in the number and function of the neurons. However, equally important in understanding the causes of the intellectual disability are the changes in the white matter of the brain that occur in Down syndrome.

What is white matter?

White matter is made up of nerve fibers covered by a sheath called myelin. Myelin is made from tightly wrapped layers of a specialized cell membrane produced by cells called oligodendrocytes, (Figure 1). Unlike the generation of neurons which happens during early fetal development, myelination, or the process of forming the myelin, begins in the third trimester and continues to early adulthood. Myelin has a high fat to protein concentration resulting in a high electrical resistance allowing it to act as insulation. This insulation speeds electrical communication to allow information to travel rapidly from neuron to neuron throughout the brain. Any disruption in myelination disrupts this electrical communication and can contribute to intellectual disability.

How is white matter changed in Down syndrome?

Numerous studies have identified changes in white matter in people with Down syndrome. A delay in the onset of myelination that averaged 12 months behind typically developing individuals was identified in children with Down syndrome (Wisniewski and Schmidt-Sidor, 1989). In addition to the developmental delay, the density of the final myelinated axons is decreased in DS (Abrahám et al., 2012; Olmos-Serrano et al., 2016). This indicates that there is less insulation which can slow neuronal communication. While the decrease in final white matter is clear, there have been conflicting reports about changes in the number of oligodendrocytes (Kanaumi et al., 2013) leaving the cause of the decreased white matter in Down syndrome still unclear.

How do we study the white matter changes?

It is clear from human studies that there is a deficit in white matter in people with Down syndrome but it is not clear how it occurs. Work in a mouse model of Down syndrome suggests that the issue is an oligodendrocyte maturation deficit (Olmos-Serrano et al., 2016). Together, tissue studies are informative, and mouse models can give good insight into potential mechanisms driving the changes, but both systems are limited if the goal is to understand the cellular and molecular changes that drive alterations in humans with Down syndrome. To get around these limitations, induced pluripotent stem cells (iPSCs) can be used. iPSCs are cells that originate from a living individual and are reprogrammed to a stem cell state which allows them to make any type of cell in the body. They are a powerful model system as they can be experimentally manipulated like mouse models but have the same genetics as humans. For the following work, I differentiated iPSCs with and without trisomy 21 into oligodendrocytes and allowed them to mature. This allowed me to assess changes in development at several different timepoints to study potential cellular causes of the white matter deficit in Down syndrome.

Changes in oligodendrocyte production in Down syndrome

Oligodendrocytes are produced by neural progenitor cells. The neural progenitor cells are activated by a signaling molecule called Sonic hedgehog (SHH) which allows the expression of two important genes: *OLIG2* and *NKX2.2* (Lu et al., 2000). On their own, *OLIG2* and *NKX2.2* are important patterning genes for making different types of neurons, but the co-expression of OLIG2 and NKX2.2 in the same cell is necessary for the differentiation of oligodendrocytes from neural progenitor cells (Zhou et al., 2001). A strong cellular response to the initial SHH signal is what allows the co-expression of both genes (Danesin et al., 2006).

In our experimental system, when the neural progenitor cells made from iPSCs were activated by SHH, the cells with trisomy 21 expressed more OLIG2 and less NKX2.2 than the control cells (Klein et al., 2022). *OLIG2* is located on chromosome 21 which might be the cause of the increased OLIG2 expression. However, it has also previously been reported that trisomic cells are less responsive to SHH signaling (Roper et al., 2006). Indeed, when we increased the strength of the SHH signal in our cell culture, the amount of OLIG2 and NKX2.2 expression was the same between the trisomic and control cells even though *OLIG2* was still triplicated (Klein et al., 2022). This initial change in expression of two important genes may alter the proportion of different cells in the brains of people with Down syndrome. It has previously been reported that there are more inhibitory neurons in the brains of people with Down syndrome which might be driven by the prolonged independent expression of OLIG2 and NKX2.2 It is also possible that there is a delay in oligodendrocyte production as there needs to be a stronger response to the SHH signal before they are made. Together these early changes may start the alterations in cell proportion that contribute to the intellectual disability.

Changes in oligodendrocyte maturation in Down syndrome

While oligodendrocyte development begins by responding to a SHH signal, full production and maturation of the cells is a long process. When we assessed the number of oligodendrocytes produced by the end of the differentiation process, there was no change in the final number produced between our cells with and without trisomy 21. However, after we allowed them to mature, we did find a significant decrease in the number of mature oligodendrocytes in the cells with trisomy 21 (Figure 2). This is important as only fully mature oligodendrocytes will produce the myelin needed to insulate the neurons. If the cells with trisomy 21 are not able to mature correctly to produce myelin, this might be the ultimate cause of the decreased white matter in the brains of people with Down syndrome. More work is needed to understand what is driving the maturation changes, but it is an exciting direction of study.

Take home messages:

- Myelin, the electrical insulator of nerve fibers in the brain, is decreased in Down syndrome and may contribute to the intellectual disability.
- The decrease in white matter might be caused by a maturation deficit in oligodendrocytes, the cells that make white matter
- The formation of white matter is a process that occurs throughout childhood and adolescence making it a viable therapeutic target. There are several FDA approved drugs that are in clinical trials to test if they increase white matter in Multiple Sclerosis.

Further reading

Klein, J.A., Haydar, T.F. (2022) "Neurodevelopment in Down Syndrome: Concordance in Humans and Models." Frontiers in Cellular Neuroscience. https://doi.org/10.3389/fncel.2022.941855 – Comprehensive scientific review of cellular changes that could contribute to the intellectual disability in Down syndrome.

https://clinicaltrials.gov/search?term=clemastine – listing of different clinical trials targeting white matter regrowth in Multiple Sclerosis

Nasrabady, S.E., Rizvi, B., Goldman, J.E. et al. (2018) "White matter changes in Alzheimer's disease: a focus on myelin and oligodendrocytes." Acta Neuropathol Commun 6, 22. https://doi.org/10.1186/s40478-018-0515-3 - Scientific review looking at the contribution of white matter to Alzheimer's Disease.

Figure 1 – Myelin is the electrical insulator of nerve fibers in the brain
Oligodendrocytes (purple) produce a special cell membrane that tightly wraps around neurons (yellow) called myelin. This combination of neurons and myelin is called white matter. Myelin acts as an electrical insulator and speeds electrical communication between neurons. (Figure produced in BioRender: CB27GW63OL)

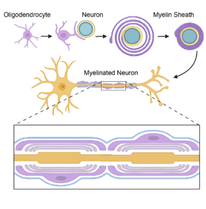
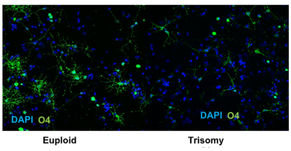


Figure 2 – Decreased maturation of oligodendrocytes with trisomy 21
The euploid oligodendrocytes (left) show an increased amount of O4 staining compared to oligodendrocytes with trisomy 21 (right). O4 is a marker of maturing oligodendrocytes.



Euploid Trisomy

References

Ábrahám, H., Vincze, A., Veszprémi, B., Kravják, A., Gömöri, É., Kovács, G.G., Seress, L., 2012. Impaired myelination of the human hippocampal formation in Down syndrome. Int. J. Dev. Neurosci. Off. J. Int. Soc. Dev. Neurosci. 30, 147–158. https://doi.org/10.1016/j.ijdevneu.2011.11.005

Danesin, C., Agius, E., Escalas, N., Ai, X., Emerson, C., Cochard, P., Soula, C., 2006. Ventral Neural Progenitors Switch toward an Oligodendroglial Fate in Response to Increased Sonic Hedgehog (Shh) Activity: Involvement of Sulfatase 1 in Modulating Shh Signaling in the Ventral Spinal Cord. J. Neurosci. 26, 5037–5048. https://doi.org/10.1523/JNEUROSCI.0715-06.2006

Kanaumi, T., Milenkovic, I., Adle-Biassetted, H., Aronica, E., Kovacs, G.G., 2013. Non-neuronal cell responses differ between normal and Down syndrome developing brains. Int. J. Dev. Neurosci. 31, 796–803. https://doi.org/10.1016/j.ijdevneu.2013.09.011

Klein, J.A., Li, Z., Rampam, S., Cardini, J., Ayoub, A., Shaw, P., Rachubinski, A.L., Espinosa, J.M., Zeldich, E., Haydar, T.F., 2022. Sonic Hedgehog Pathway Modulation Normalizes Expression of Olig2 in Rostrally Patterned NPCs With Trisomy 21. Front. Cell. Neurosci. 15, 541. https://doi.org/10.3389/fncel.2021.794675

Lu, Q.R., Yuk, D., Alberta, J.A., Zhu, Z., Pawlitzky, I., Chan, J., McMahon, A.P., Stiles, C.D., Rowitch, D.H., 2000. Sonic hedgehog–regulated oligodendrocyte lineage genes encoding bHLH proteins in the mammalian central nervous system. Neuron 25, 317–329.

Olmos-Serrano, J.L., Kang, H.J., Tyler, W.A., Silbereis, J.C., Cheng, F., Zhu, Y., Pletikos, M., Jankovic-Rapan, L., Cramer, N.P., Galdzicki, Z., Goodliffe, J., Peters, A., Sethares, C., Delalle, I., Golden, J.A., Haydar, T.F., Sestan, N., 2016. Down Syndrome Developmental Brain Transcriptome Reveals Defective Oligodendrocyte Differentiation and Myelination. Neuron 89, 1208–1222. https://doi.org/10.1016/j.neuron.2016.01.042

Roper, R.J., Baxter, L.L., Saran, N.G., Klinedinst, D.K., Beachy, P.A., Reeves, R.H., 2006. Defective cerebellar response to mitogenic Hedgehog signaling in Down [corrected] syndrome mice. Proc. Natl. Acad. Sci. U. S. A. 103, 1452–1456. https://doi.org/10.1073/pnas.0510750103

Wisniewski, K.E., Schmidt-Sidor, B., 1989. Postnatal delay of myelin formation in brains from Down syndrome infants and children. Clin. Neuropathol. 8, 55–62.

Zhou, Q., Choi, G., Anderson, D.J., 2001. The bHLH transcription factor Olig2 promotes oligodendrocyte differentiation in collaboration with Nkx2.2. Neuron 31, 791–807. https://doi.org/10.1016/S0896-6273(01)00414-7