Neurogenesis, Myelination and Circuitry:

The case for a distributed therapeutic regimen in Down syndrome.

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Background

Trisomy 21, or Down syndrome (DS), is caused by triplication of chromosome 21 and occurs in ~1:700 live births. Many areas of the body are affected by the trisomy, including the cardiovascular, gastrointestinal, respiratory and nervous systems. While many of these issues can be addressed medically or surgically, the intellectual disability (ID) found in people with DS is not very well understood. Many labs across the world are actively studying the causes of these changes in the hopes of finding therapies to improve the level of independence and quality of life for people with DS.

Thus far it is clear that alterations in the brain and spinal cord are first seen prior to birth, when the cells of the nervous system are produced by stem and progenitor cells in select areas of the developing fetus. These early changes are followed by decreases in the overall size of some brain regions and by changes in the functional communication within and between brain areas. In addition, beginning in their 40's, people with DS develop plaques and tangles in their brains that resemble those found in Alzheimer's disease (AD); the dementia that can then ensue is an additional hardship for adults with DS, their families and caregivers. Here, I hope to provide a brief picture of the many areas of nervous system development and function that have been implicated in DS and to show how these changes occur at different times and by different

mechanisms. Altogether, the findings suggest that addressing multiple deficits when they arise may provide the best strategy for improving quality of life for people with DS.

Advances & Challenges

Often the most successful solution to a problem, whether it is an engineering problem, a social problem, or a biological problem, is to find its core, or first instance, and then prevent it from occurring in the first place. For DS, this approach is challenging for two main reasons: first, the initial cause of the disorder is the triplication of ~300 genes, many of which are not well understood, and they lead to altered expression of many more hundreds of genes found throughout the rest of the genome (Letourneau et al. 2014; Olmos-Serrano et al. 2016). Second, these genetic changes occur at conception, and while some of the genetic networks that are altered in DS may not manifest until many years later, the first event affects the very earliest moments of life. While fetal therapy may soon be accepted as a rational choice (de Wert et al. 2017; Stagni et al. 2015), methodological approaches and their associated ethical guidelines remain to be established. Another approach to addressing the causes of ID is to carefully catalog the many changes occurring in people with DS across their lifetimes, so that each challenge they face can be organized into a temporal sequence with a clear biological cause.

The neurons in the developing brain are born in specialized germinal zones surrounding the cerebral ventricles and have to migrate long distances to reach their proper location prior to maturation. In addition to the reduced production of neurons in the developing brains of people and animal models of DS (Aziz et al. 2018; Chakrabarti et al. 2007; Contestabile et al. 2007), positioning of these cells does not occur properly in some regions of the neocortex, indicating

that neuronal migration may also be affected in DS (Haydar and Reeves 2012). After birth, the neurons and glial cells mature and form the intricate and long-lasting network of circuits that underlie neurological function. It is during this process that the first behavioral deficits are seen in babies and toddlers with DS, namely the widespread occurrence of hypotonia and delayed acquisition of developmental milestones such as rolling over, talking, walking, etc. Over the course of infancy and adolescence, deficits in cognition, learning and memory are also observed and join the changes in fine and gross motor function.

One common finding in mouse models and in postmortem human studies is that the ratio of excitatory to inhibitory neurons is altered, leading to alterations in excitability of the neural circuits. However, it is unlikely that this or any other single change could explain all of the above symptoms. In fact, postmortem brain studies indicate that multiple gene networks are disturbed at different stages of life in DS (Olmos-Serrano et al. 2016), suggesting that many of the phenotypes in DS are caused by separate developmental processes. One of the disturbed gene networks found recently is involved in promoting the development of oligodendrocytes, the cells that produce the myelin that insulates the long pathways of axons in the brain. Work in mouse models of DS indicate that this reduced myelin production and maintenance is associated with slower neuronal communication speeds due to the lack of insulation.

Outlook

It is known that myelination is a process that begins in the third trimester of fetal development and continues until the mid-20's in the human brain. Thus, promoting oligodendrocyte maturation and myelin production may be a reasonable approach to improving

cognition in DS, and the large duration of myelination in the human brain indicates that such an approach would have a long therapeutic window.

The increased incidence of AD-like pathology and dementia in DS may have different origins from the brain alterations discussed above. Triplication of the *Amyloid Precursor Protein* gene and increased brain immune activation may play roles, but exactly how and when they may do this is still not known. Discovering when and how the pathology occurs is critical for developing a future therapy. It is likely that adult stages of life will need to be targeted to address the AD pathology.

Taken together, many cellular and molecular processes change in the brains of people with DS both before and after birth and it will be necessary to develop a suite of possible therapies to counteract these changes. It is important to recognize that people with DS are all different and that the levels and locations of their disabilities are also different. Thus, establishment of a series of possible therapies would enable individualized treatment options.

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