EDITORIAL

The Struggle of Neural Progenitors in Down Syndrome Brain: The Need for Neuromodulation Beyond Symptomatic Mitigations

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Down syndrome (DS) is a chromosomal disorder that occurs at a rate of 1 in every 1000 live births in all ethnic groups (1). In Malaysia, the incidence of DS is one in 950 live births (2). Individuals with DS have an extra chromosome 21, the most prevalent genetic cause of intellectual disability and characterised by various dysfunctions in neurodevelopment, growth, and cognitive and psychomotor impairments. While intellectual disability, hypotonia and craniofacial dysmorphism are the well-recognised cardinal phenotypes of Down syndrome, the genetic disorder is also burdened with a broad spectrum of co-morbidities such as accelerated ageing, early-onset Alzheimer's disease, leukaemia, heart defect, gastrointestinal disorders and as much as 80 more different clinical manifestations throughout all stages of their life (3).

Learning disability is the hallmark of DS and is usually due to delayed cognitive development during early infancy. The severity of the learning disability varies among DS individuals, with an IQ score ranging from 30 to 70 with an average score of 50 (4,5). Their IQ declines with age (6,7) due to accelerated ageing (8,9). Learning, memory and language appear to be affected significantly in individuals with DS, where learning disabilities affect long-term and short-term memory formation (10,11). To date, several hypotheses have been proposed to explain the DS phenotype, including gene dosage imbalance (3,12), the amplified developmental instability hypothesis (13), and the Down syndrome critical region (DSCR) hypothesis (14). However, none of the hypotheses was fully proven to cause the neuropathologies seen in DS, especially those that led to intellectual disabilities and accelerated cognitive decline.

Morphologically, the DS brain has a reduction in brain weight and brain volume (15). Newborn infants diagnosed with DS have reduced volume in several brain regions, such as the prefrontal cortex, amygdala, cerebellum, and brain stem (16). The neuroanatomic changes in the DS brain suggested that it was caused by defective neurogenesis during brain development. Analysis of the dentate gyrus, hippocampus and parahippocampal gyrus of foetuses with DS showed that the proportion of neuronal populations was less than the control foetuses (17). In addition, the precursor cell for cerebellar neurons originating from the external granular layer and ventricular zone showed impaired proliferation (18). A study performed on neurospheres derived from the subventricular zone of an adult Ts1Cje (a mouse model for DS) mouse brain also demonstrated that the numbers of the neurone were reduced by approximately 56% (19) or with smaller diameter (20) compared to sex-matched disomic littermate controls. These findings indicated that the neuronal loss in the DS brain is associated with proliferation deficits and apoptosis of neural progenitor cells (NPCs), leading to reduced neurogenesis (21).

The number of astrocytes was increased in human foetuses with DS. Immunohistochemical staining of the frontal lobe of human foetuses DS brain showed increased GFAP-positive cells compared to the age-matched controls (22). The finding was consistent with a previous study on both human foetuses and Ts65Dn mouse brains for DS (17,23). A study by Chen and colleagues, DS astroglia, introduced a negative impact on neurogenesis, where it caused toxicity to the neurones and induced neuronal cell death (24). Although gliogenic shift has a toxic effect on the DS brain, overall, the aetiology and consequences of neurogenic-to-gliogenic shift where the NPCs tend to differentiate into glial cells than neurons in the DS brain remain understudied, especially in the early stage of brain development. The neurogenic-to-gliogenic shift causes neurone-to-astrocyte ratio imbalance in DS, leading to insufficient or lesser neurones to begin within a somewhat more hostile environment comprising more reactive astrocytes and microglia.

The neurogenic-to-gliogenic shift in DS is characterised by the preferential acquisition of astroglial cell fate by NPCs. Increased astroglial cell fate commitment in DS is accompanied by astrogliosis, reduced neurogenesis, abnormal oligodendrocyte differentiation, and hypomyelination (21,25). The number of astrocytes is increased in various mouse models as well as in human foetuses with DS (17,22). Astrocytes in DS are not only more proliferative and abundant, but they also display altered processes (26). Increased astrocyte reactiveness and activity were observed in DS-iPSC-derived astrocytes as determined by increased spontaneous calcium fluctuations that impede neuronal cell excitability (27). In addition, increased reactive oxygen species (ROS) were found in DS astrocytes, and the DS astrocytic conditioned media caused neurotoxicity, impaired ion channel maturation and synaptic development (24). Hyperactivation of the Akt/mTOR signalling pathway in both DS astrocytes and neurones were observed and potentially contributed to neuronal abnormalities and cell-autonomous dysfunctions (28).

In the frontal cortex of DS children and young adults, microglia were found to have a higher microglial soma size-to-process length ratio and appeared rod-like in shape (29). The morphology of microglia evolved over the lifespan of DS individuals as determined by the appearance of the cell and the coincidental dysregulation of various cytokines (29). The findings of an early and evolving neuroinflammatory phenotype across Down syndrome's lifespan are potentially relevant to understanding Alzheimer's disease onset and progression in this population. Gain-of-function of a trisomy 21 gene known as Usp25, a deubiquitinating enzyme, caused microglial activation and led to synaptic and cognitive deficits in 5XFAD mice, a model for AD. When Usp25 was ablated, reduced neuroinflammation and improved synaptic and cognitive function were observed in the mouse model (30). Similarly, activated microglia with increased pro-inflammatory cytokines and altered interferon signalling were documented in the hippocampus of the Dp(16) mouse model for DS and DS individuals (31). The observations were characterised by decreased spine density and reduced neuronal activity, and neuropathological phenotypes were reversed when defective microglia were treated with anti-inflammatory drugs (31). Taken together, both astrocytes and microglia are equally affected by trisomy 21. Their roles in neuroinflammation and the regulation of dendritogenesis, neuritogenesis and synaptogenesis in the nervous system suggest that astrocytic and microglial dysfunction contributes to cognitive impairment in DS.

Pro-inflammatory cytokines, such as IL-6, TNF-alpha, and TGF-beta, were at least 2-fold higher in autopsied human DS brain tissues (<40 years old) when compared to age-matched controls (32). These cytokines are well-known activators of the JAK-STAT signalling pathway, a neuroinflammation regulatory pathway mediated by upstream interferons or interferons receptors. The extra copy of the IFN receptor and the elevation of IFN level have been postulated to sensitise the cells to interferon interaction and lead to activation of the JAK-STAT signalling pathway in astrocyte as well as microglia (33-35), turning them from the resting into the reactive form. Activation of glial cells could lead to neuroinflammation via the release of nitric oxide (NO) (36,37). The gene expression level of inducible nitric oxide synthase (iNOS) that stimulates NO generation was higher in DS astroglia than in control astroglia (24). In addition, increased ROS and tau hyperphosphorylation were observed in primary cultures of hippocampal neurons and astrocytes derived from Ts1Cje, a mouse model for DS (38). Increased ROS was accompanied by mitochondrial dysfunction in the DS brain, such as morphological defects (damaged cristae, enlarged size, reduced volume), impaired biogenesis and dynamics (reduced mass, reduced fusion, increased fission, hyperfused network) and perturbed metabolisms (increased apoptosis, reduced electron chain activity, reduced respiration, oxidative phosphorylation, reduced ATP production, reduced membrane potential and increased ROS) (Tan et al., unpublished). Taken together, the DS brain is constantly placed in a greater neuroinflammatory environment due to increased gliosis compared to the control brain. It remains hard to predict whether the DS brain suffers from an intrinsic neuroinflammation condition or merely fails to adapt to stress due to dysfunctional resilience mechanisms.

A multifaceted approach is a must to understand the neurogenic-to-gliogenic shift and the reactivity of both astrocytes and microglia in the DS brain. Early neuromodulation of neural progenitors' fate would help revert the neurone-to-astrocyte imbalance and potentially mitigate neuroinflammation in the brain. A JAK1 and JAK2 inhibitor, ruxolitinib, was recently repurposed to suppress the JAK-STAT pathway in mice during gestational development (39). Pups from the treated pregnant mice were significantly less anxious and performed better in spatial and long-term memory tests suggesting that early modulation during pregnancy effectively improved intellectual capabilities. Ruxolitinib is the first anti-cancer drug to improve neurogenesis; such observation is merely the tip of the iceberg. The study has opened the pandora box to various possibilities of transplacental pharmacotherapy for early neuromodulation that may have a significant outcome for the DS community. While more thorough investigations must be performed to evaluate the daring strategy, DS individuals deserve more than symptomatic treatments or rehabilitation for an improved quality of life. They deserve a potential cure with permanent alteration to improve their intellects, quality of life, build a happy family and capability to contribute to society and nation.

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