Current Research Approaches to Down Syndrome: Translational Research Perspectives

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Background

Translational research means different things to different people. In the biomedical research community translational research is the process of applying knowledge from basic biology and clinical trials to techniques and tools that address critical medical needs such as new therapies. Translational research then is a “bench to bedside” bridge specifically designed to improve health outcomes (Wetmore & Garner 2010). In this sense animal models or cell culture systems may be used to learn about basic underlying genetic and physiologic systems that are exceedingly difficult to study in human subjects (Reeves et al. 2019). This has been a major theme in Down syndrome (DS) research since the mid-1980s when mouse models that approximate the condition of trisomy 21 (Ts21) first became available (Das & Reeves 2011).

Translational research has recently taken on a more expansive meaning, as the process of turning observations from the laboratory, the clinic and the community can all lead to new therapeutic approaches to improve population health outcomes (Rubio et al. 2010). This model has received increased attention in the last decade as it is clear that improving developmental outcomes for people with DS requires a community effort on the part of all stakeholders (Capone 2010)

Advances

Behavior phenotype(s). It remains startling that despite the common theme of Ts21, the differences between individuals is often striking, particularly cognitive functions that emerge

throughout brain development-organization and maturation. While no single behavior-phenotype**,** other than perhaps intellectual disability itself, describes all individuals with Ts21, there are several recognizable variations on this theme. The study of within-syndrome variability in cognition, behavior, language, and adaptive function constitutes a major intellectual challenge to those researchers who evaluate substantial numbers of individuals. The use of existing behavior rating scales and the promise of new ones will take us deeper into the realm of what we mean by phenotype and how this evolves from childhood through adolescence and into adulthood. There are implications here that inform our approaches to early intervention, no longer one-size-fits-all; to defining the boundaries and intersections between character trait (phenotype), behavioral impairment (maladaptive), and mental illness (psychopathology).

Vulnerable brain. As a model of gene dosage imbalance with complex gene-gene and protein-protein interactions, the manner in which brain organization is disrupted in Ts21 matters. ID and related dysfunctions probably arises through numerous neurobiological processes including progenitor and stem cell defects that impact neurogenesis and gliogenesis; impaired dendritic growth and synaptic spine formation and plasticity; and reduced connectivity at both the ultrastructural and circuit levels (Bartesaghi et al. 2015) (Pujol et al. 2015).

Yet, the idea of a more *vulnerable brain* as a longer-term consequence of disordered development and subsequent dysmaturation has been little explored. It is possible that certain brain circuits that are already underpowered and underperforming actually become 'malnourished' under physiologically averse conditions, placing them at risk for functional decompensation (Pujol et al. 2015), (Worley et al. 2014), (Penzes et al. 2013). Given what we know about the effects of seizures and chronic sleep disturbance, it is not beyond our grasp to

ask why such individuals are more prone to behavioral, mental health and cognitive deterioration (Tapp, Anderson, & Visootsak 2015), (Capone et al. 2013), (Cha et al. 2017)

Neuromaturation. In individuals with Ts21, the prefrontal cortex (PFC) and its connections are a particularly vulnerable brain region because of prolonged maturational timeline and complex circuitry. Disruption thereof manifests itself in highly debilitating behavioral impairments and related manifestations. While the PFC is a relatively recent adaptation, the critical developmental mechanisms that drive its maturational timetable are no doubt highly conserved, but not so well buffered throughout maturation. It appears that the period of sensitivity to both environmental and genetic perturbation extends throughout childhood and well into adolescence (Dahl 2004), (Caballero, Granberg, & Tseng 2016), thus increasing the window of vulnerability. Significantly, gender differences in the developmental timetable are apparent in typically developing children and several neurodevelopmental disorders (Shaw et al. 2007), (Shaw et al. 2006), (Shaw, Gogtay, & Rapoport 2010), (Jahanshad & Thompson 2017).

Future Outlook

Medical model. Recent biomedical literature discusses the prospect of prenatal or early postnatal intervention to prevent developmental neurocognitive impairments in Ts21 (Guedj, Bianchi, & Delabar 2014). Using mouse models, this work is exciting and novel (Nakano-Kobayashi et al. 2017). However, despite better understanding of critical mechanisms, such insights are always difficult to translate into safe and effective treatments for human subjects. Most medical interventions seek to relieve dysfunction or to stabilize/preserve existing function in people with illness. People with DS are prone to a variety of different medical illnesses and conditions throughout their lives, and prevention of illness or dysfunction is a worthy goal to

strive for. Supported by the conceptual understanding that Ts21 leads to genome-wide dysregulation researchers have sought to find the necessary switches to turn these mechanisms down in an effort to prevent the phenotypic consequences of Ts21 that we recognize in DS (Antonarakis 2017), (Chiang et al. 2018).

As for all new therapeutic prospects, individual stakeholders (researchers, industry executives, advocacy representatives, physicians and parents) are likely to have very different motivations for or against moving forward with such endeavors. Few studies of parent attitudes have been conducted, but in one involving 101 parents from British Columbia, 61% viewed the idea of reversing ID positively, 41% replied they would use such a therapy if available to "cure" their child of DS itself, 27% would not seek to cure their child, and 37% were unsure (Inglis et al. 2014). The reasoning behind these answers is complex. The parents surveyed represented both young and adult children with DS, however adults with DS themselves were not included in the survey. Interestingly, 43% of parents thought that researchers should be looking to cure DS itself, while 33% were unsure. And so these research efforts will continue. That which motivates parents of children with DS to be at their very best is nothing new; hopeful thinking runs deep in us all. Even if it were possible to prevent ID in DS, and it is not currently, the parents of children born and unborn will be the ones to decide which therapeutic options are adopted, and for whom, based on very personal reasons.

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