Cellular therapy for autism spectrum disorder: a step forward to the optimal treatments

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The widespread prevalence of Autism Spectrum Disorder (ASD), as indicated by the most recent report from the US Center for Disease Control in 1 autistic child on 59 children (1), recalls for novel research investigations and prospective treatments. This complex and heterogenous neurodevelopment disorder still does not have a known pathogenesis. Recently, the contribution of the environment on epigenetics mechanisms of ASD has been proposed (2), together with persistent inflammation state and important cellular and molecular changes in neuro-immune systems cross-talk (3,4). Currently, available treatments are only directed on behavioral, occupational and speech interventions, and there are no agreed upon therapeutic approaches for either the core behaviors or the associated comorbidities (5).

The intrinsic capacities of stem cells offer novel approaches for neurodegenerative diseases (6) and make them promising candidates also for ASD treatment (7). Indeed, cell-based therapies have been proposed and applied to ASD to address the neurobiological changes underlying its development and progression.

The authors Carpenter *et al*. described, in their paper published in *Stem Cell Translational Medicine* on January 08, 2019, the use of autologous umbilical cord blood (AUCB) for the treatment of ASD, also providing brain targets for the elucidation of higher centres involved in ASD development (8).

Safety and effectiveness of this type of cell transplantation were already demonstrated by the authors in a precedent interesting publication, reporting the results of a phase I, single-center, open-label study on the use of autologous umbilical cord blood transplantation in 25 ASD children (9). In that study, a single intravenous infusion of AUCB was transplanted in each ASD subject, without serious adverse effect reported in any participant. In addition, socialization, communication, and adaptive behavior scores were improved at 6 months post-infusion and were sustained between 6 and 12 months post-treatment (9).

In this new research article (8), the positive outcomes of AUCB transplantation in ASD children in increasing social functioning and communication abilities were associated to increased white matter connectivity in brain networks. This latter point is a key factor in ASD development, as brain connectivity and synaptic density have been demonstrated to be disrupted in ASD subjects, as well as in animal models of autism (10,11). In the study, each ASD participant received an infusion of the own cord blood unit ($1–5\times10^7$ cells/kg) and was followed up at 6 and 12 months post-transplantation. They were scanned by magnetic resonance imaging and structural connectome analysis was performed. According to authors, significant correlations were found between increases in the connectivity between pairs of brain regions and behavioral improvements. Increased brain frontal, temporal, and subcortical white

matter connectivity post-AUCB treatment was associated to increase in behavioral improvements and increased child cognitive levels. The increased brain connectivity after cellular therapy involves specific areas of ASD-related symptoms. In example, post-cellular therapy clinical improvements and increased social skills were associated with increased connectivity between the left thalamus and the hippocampus, whereas increased connectivity between the superior temporal sulcus and the putamen was parallel to the improvements in social communication and language abilities (8). These findings also indicate that ASD subjects show altered brain connectivity, and that specific ASD symptoms are associated to the altered connectivity between specific brain structures. These results well fit with the other findings obtained by functional magnetic resonance imaging studies showing that ASD subjects display decreased connectivity among frontal and more posterior brain regions affecting language comprehension, spatial processing, face recognition and working memory (the so-called under-connectivity theory of autism) (12,13). Importantly, white matter pathways are less developed in ASD individuals, with abnormal white matter growth during the life time (12). From an anatomical perspective to a cellular level, post-mortem brains from ASD subjects show changes in synaptic organization and spreading, as well as alterations in neurotransmission systems (14). Astrocytic and microglia cells show alteration in their functions in ASD brain, together with abnormal increase of pro-inflammatory cytokine levels. Neuroinflammation is linked to brain connectivity.

As possible mode of action, authors suggest that AUCB-treatment decreases neural inflammation, in this way promoting the development of white matter connectivity in neural networks. This is in line with the stem cell characteristics. In addition, even if the authors did not in depth characterize the cells in the umbilical cord [the cells were CD34+, indicating a probable, but not definitive, hematopoietic origin (15)], the source of the stem cell used offers several great advantages: stem cells extracted from umbilical cord and/or placenta display mesenchymal characteristics (16). Low immunogenicity and immunomodulation properties rend them optimal for applications in ASD (7). In addition, no teratoma formation has been found. Furthermore, stem cell could address inflammation through their paracrine effect (the secretome machinery: cytokines, chemokines, and growth factors released by stem cells and responsible of repair/restoration of injured tissues) and immunomodulatory properties (7). It is also noteworthy to consider that increased neurogenesis after mesenchymal stem cell transplantation has been demonstrated in two animal models of autism (17,18).

The reported results encourage starting of placebo-controlled double-blind trials. However, several limitations should be faced before claiming definitive conclusions for cellular therapy in ASD (7).

In this referenced study, for cellular transplantation a part of or entire umbilical cord was used, a better characterization of specific cellular sub-types would help in future choice of cells to be used in clinical settings. Another question is if the cells require *in vitro* cultured expansion before transplantation.

By an ethical point of view, the autologous transplantation requires preventive storage of the own biomaterial of the future patient. This raises concerns about proper bio-banking and the cost for the cryostorage. In some cases of genetic modifications present in the ASD patient, stored and bio-banked cell types will conserve the genetic changes. In these cases, even if limited, allogenic transplantation should be to prefer rather than autologous one (7).

In conclusion, this current research article (8) indicates encouraging positive outcomes of cellular therapy in ASD, providing potential benefits for this type of approach. In addition, it reports important advances for the comprehension of the anatomical pathways involved in ASD pathophysiology, also contributing to the elucidation of the mechanisms by which cellular transplantation leads to an enhanced functional recovery and structural brain reorganization.

These results advocate for the use of cellular therapy in ASD. More large placebo-controlled double-blind trials and exhaustive investigations will be needed in order to conclude for definitive results.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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