Role of Stem Cells in Autistic Spectrum Disorder (ASD); Can it Change the Future?

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ABSTRACT

Autistic spectrum disorder (ASD) is a group of disorders described by disabled social connection and serotyped conduct, interests and activities causing gross functional impedance. The precise pathogenesis, etiology, genetic involvement, and treatment are as yet under study. The absence of accessibility of live patient-particular neurons has been a substantial limitation in contemplating ASD pathophysiology. The ongoing utilization of induced pluripotent stem cells (iPSCs) to produce the human neurons from somatic cells, has altered the field of research for better understanding the distinctive aspects of ASD. In this article, we featured the fundamental properties of stem cells, conceivable sources, gene articulation, differentiation pattern, immune-modulatory impacts, safety issues and route of administration. We likewise talked about conceivable mechanisms of pathogenesis, i.e. changes in neural structure, genetic variability, molecular varieties, immune hyperactivity state and hypo-perfusion of the brain. Remedial intercessions concerning drug screening and transplantation treatment in the various setting have additionally been assessed, quickly.

INTRODUCTION

Autism spectrum disorder, as characterized in the DSM-5[1] alludes to four previously distinctive neurodevelopmental diagnoses including autism, Asperger syndrome, childhood disintegrative disorder, and pervasive developmental disorder-not otherwise specified (PDD-NOS). Syndromic forms of ASD contain disorders with a known, usually monogenetic, cause including fragile X syndrome (FXS), Timothy syndrome (TS), cyclin-dependent kinase-like 5 disorder, and Rett syndrome (RTT). Conversely, non-syndromic, or idiopathic, forms of autism, do not have a known genetic etiology. It usually presents at the age of 2 years with a child lacking behind the standard growth curve and unfit to achieve normal reflexes and skills(e.g., some patients do not express social smile)[2]. The cause of ASD is obscure and making it challenging for disclosure of appropriate cure for the disease. The U.S. Food and Drug Administration presently cannot seem to favor a single drug for the treatment of autism's core symptoms. There is no diagnostic test available[3]. At present accessible treatments for autism can be divided into behavioral, nutritional, and pharmacological options, in addition to individual and family psychotherapy and other non-pharmacologic remedies[4]. Psycho-stimulants, alpha-2 agonists, beta blockers, lithium, anticonvulsant mood stabilizers, atypical antipsychotics, traditional antipsychotics, selective serotonin reuptake inhibitors, antidepressants, and antipsychotics, are drugs commonly prescribed[5–7]. Catatonia is treated with lorazepam and bilateral electroconvulsive therapy[8].

In spite of the disclosure of many proposed mechanisms explaining neuron's structural changes, genetic transformations, molecular modifications and impact of environmental factors engaged with the pathogenesis of ASD, the research in this field still need good endeavors in uncovering the truth behind this myth. Sir John Gordon and Shinya Yamanaka have just been granted the Nobel Prize in 2012 for Medicine on their contribution to the reprogramming technology and featuring the noteworthiness of this logical breakthrough[9]. Since at that point, (iPSCs) have pulled in consideration of researchers, policymakers, and ethicists due to their mysterious properties. The utilization of iPSCs for understanding the pathogenesis, drug screening, and restorative perspectives has revolutionized the field of research. Now; we are a step closer for the accomplishment of desired objectives concerning the management of ASD patients. In this review, we are looking into the different aspect of stem cells utilization from various sources in

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understanding the pathogenesis, diagnostics, drug testing, and therapeutic transplantation, giving likely outcomes.

1 in 68 children and is said to be the fastest-growing serious developmental disability in the United States[3]. Through the endeavors of autism advocacy groups, ASD is presently viewed as a national health priority in the United States, with government and private subsidizing more than $400 million in 2010 [10]. In this review, we assembled data from different research articles to assess the exact role of (iPSCs) for providing a path to future researchers to recognize the advantages and disadvantages of (iPSCs) used for the helpfulness of ASD patients. We additionally assess the accessible sources of stem cells, routes of delivery, and follow up of results from different patient and advances made in drug screening and transplantation choices, consequently, presumed that there is a promising future for ASD people. Various highlights with respect to the application in large-scale cohort study are as yet inaccessible. A number of key troubles remain, including the scaling of iPSC models to bigger companions and joining with rich clinicopathological information and translation of phenotypes[11]. Large-scale screening of chemical libraries with disease-specific iPSCs and their utilization in drug testing and transplantation may give us an exceeding expectation. In light of the way that the use of iPSC innovation in disease modeling requires a known disease phenotype for exhibit of the cell model; autism research including this innovation centers around monogenic cases, for instance, Rhett Disorder, Fragile X Disorder, and Timothy Syndrome, which involve only 15 % of every single dissected case[12–15]. However, a superior future can be expected for an ASD individual by the assistive advancements made by iPSCs in the field of analytic and remedial Medicine.

METHOD AND SEARCH CRITERIA:

Source of data collection:

Do the stem cells have any role in exploring the pathogenesis, diagnosis, and management of autism? With this question in mind, the data was searched and collected. Top online databases (PubMed etc.) mainly were utilized as a source of data collection. We included only relevant studies which primarily centered on stem cell utilization in explaining pathogenesis, gene expression, drug screening, and transplantation studies.

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Inclusion criteria:

1)The studies involving subjects of autism, Asperger and pervasive developmental disorder not otherwise specified (PDD-NOS); 2) studies published in peer-reviewed journals ; 3) in English and studies involving human preferably but combined studies of human and animals also included.

Exclusion criteria:

1) If they did not mention the collection(s) in the research data, references, acknowledgments or supplementary materials; 2) If studies only concerned animal models of ASD without using/application on ASD human individuals; 3) articles not published in peer-reviewed journals; 4) studies in languages other than English.

For each article, the study material was analyzed for: a) publication status of article, (b) the article subject, (e.g. essential properties of stem cells, conceivable sources, gene expression, pattern of differentiation, immune-modulatory impacts, safety issues, routes of administration, components of pathogenesis supporting modification in neural structure, genetic variations, immune-hyperactivity state, hypoperfusion of brain, oxidative stress, inflammatory and natural environmental factors) as well as interventions with respect to drug screening and transplantation treatment completely different setting, (c) application aspects (any constraints such as journal lists, conditions, or specialties). The framework for data gathering included looking of all study references to find some other related articles not caught within the preliminary evaluation. Duplicate studies were erased utilizing advanced object identifiers and manually comparing titles, writers, production dates, and article metadata. Every single article was screened separately by two investigators for analysis, and contradiction was settled through discussion.

RESULTS

We directed this review that reveals the utilization of stem cells in deciding the ASD pathogenesis, genetic contribution and restorative mediations alongside fundamental properties, distinctive sources, and method of administration of stem cells. Articles identified with ASD and stem cells were gathered through PubMed chiefly, different sources incorporate MEDLINE,

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Journal of Neural Transmission, Oxford Journal, Psych Central, PsycINFO, Cochrane library, and different daily papers.

Keywords were chosen and searched for relevant research articles as "stem cell therapy and autism" gave 139 studies; "stem cell therapy and autistic spectrum disorder" gave 92 studies; "stem cells and autistic spectrum disorder" gave 240 studies; "stem cells and autism" gave 438 studies; "induced pluripotent stem cells and autistic spectrum disorder" gave 108 studies; "induced pluripotent stem cells and autism" gave 154 studies; hence, total of 1171 appeared. In the wake of dealing with duplicates=212, left us with 959 studies. Free full-text studies were 720 in number. A set of 387 studies remained after screening titles and abstracts, and of these, 55 studies were included in the review.
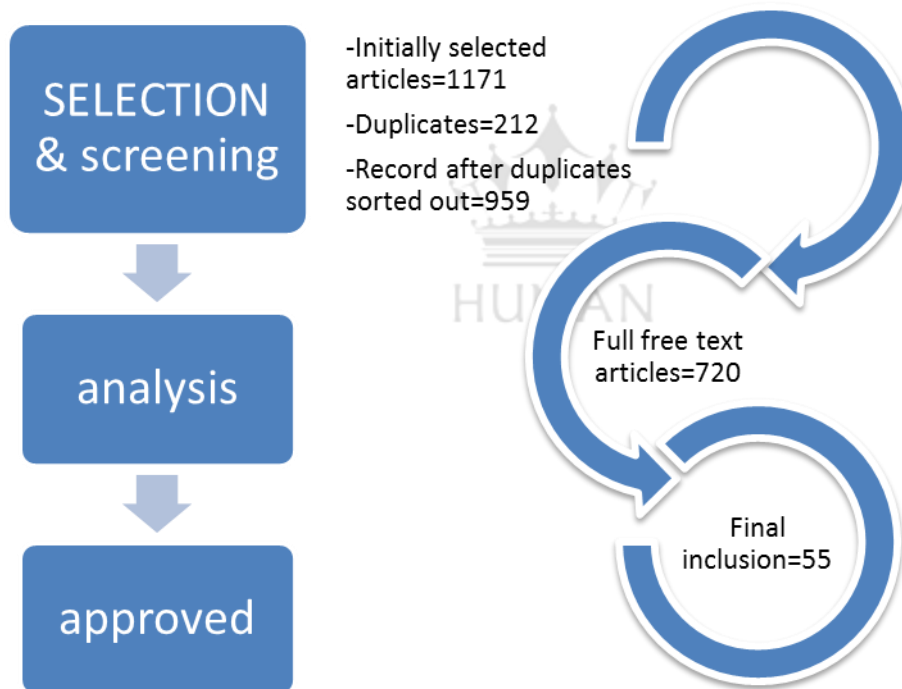
No study was incorporated into last round simply screening the abstract. The reviews with a high possibility of bias and those with obscured or blended information were avoided. Any studies published in non-popular journals were additionally barred in order to keep up the high standards of the study. A few investigations were rejected because they did not gauge interfaces between undifferentiated stem cells and autistic spectrum disorder directly.

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Data contains a sum of 4090 individuals among them 155 were children,2886 were in control group,3913 adults were used in genetic manifestation studies,25 children were utilized in medicate screening trial and 130 children alongside with ten adults were utilized in stem cell transplantation studies. The animals incorporated in the studies were rodents especially the mouse. Among genetic assessment studies, 1041 ASD individuals were found to non-synonymous mutations of TRCP6 gene when contrasted with 2878 controls[16]. Chromodomain helicase DNA-binding protein 8 (CHD8) were recognized in 12 people portraying altered expression of 1715 genes, including both protein-coding and noncoding ASD and zero controls, representing an exceedingly noteworthy association[11]. Administration of pioglitazone (PPAR-gamma agonist) in 25 children came about 75% improvement in response on aberrant behavior checklist[17]. Infusing human neural progenitor cells (hNPCs) in a group of twenty-two children with pervasive developmental disorder, including 13 children with Rett syndrome and 9 children with autism, indicates 17 patients, including 8 patients with autism and 9 patients with Rett syndrome, variable improvement. Total scores on Autism Behavior Checklist and social communication and language scores were likewise radically lessened 1 year after transplantation (P<0.05)[18]. Study of 71 children with incurable neurological disorder includes administration of bone marrow-derived mononuclear cells, 88 % of cases showed a variable level of improvement[19].

Another study involving 37 subjects diagnosed with autism with the formation of three groups: 1) combined transplantation of human cord blood mononuclear cells CBMNC group (14 subjects, received CBMNC transplantation and rehabilitation therapy); 2) Combination group (9 subjects, received both CBMNC and umbilical cord-derived mesenchymal stem cells (UCMSCs) transplantation and rehabilitation therapy); 3) Control group (14 subjects, received only rehabilitation therapy). They were accessed utilizing the Childhood Autism Rating Scale (CARS), Clinical Global Impression (CGI) scale and Aberrant Behavior Checklist (ABC). Transplantation of CBMNCs indicated efficacy contrasted with the control group; notwithstanding, the blend of CBMNCs and UCMSCs delineated more significant restorative impacts than the CBMNC transplantation alone[20].

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DISCUSSION

Definition of MSC:

Concurring to the International Society of Cellular Therapy, MSCs are characterized by the following minimal set of criteria: (1) competent of developing in adherence to plastic surface of dishes under standard culture conditions; (2) show cyto specific cell surface markers, i.e. CD105, CD90, and CD73, to be negative for other cell surface markers, i.e. CD45, CD34, CD14, and CD11b; (3 have the capacity to distinguish into mesenchymal lineages, under appropriate in vitro conditions[21]. Stem cells are nonhematopoietic (of mesodermal in origin) having a multilineage potential, as they are capable of differentiating into both mesenchymal and non mesenchymal lineages, primarily found in the bone marrow of adults, giving rise to skeletal muscle cells, blood, fat, vascular, and urogenital systems, and to connective tissues throughout the body.

Source of stem cells

Embryonic stem cells

Origin of embryonic stem cells (ESCs) takes place from early stages of embryonic development[22,23], fit for differentiating into hematopoietic cell lineages, offering to ascend to all blood cell types and subtypes of the immune system (i.e. T cells, NK cells, and dendritic cells)[24,25]. Rejection is shown in cases by recipient immune system when HLA-II expression occurred[26]. Paracrine activity is observed at the embryonic stage of their development[27].

Fetal stem cells (FSCs)

Fetal mesenchymal stem cells apply immunomodulatory impacts[28] and show less degree of senescence. In contrast to ESCs, they are incapable of converting into teratomas posttransplantation[29] and have a better capacity to differentiate into pluripotency than neonatal and adult cells[30]. Rather than MSCs, in early stages FSCs demonstrate pluripotency stem cell markers Nanog, Oct-4, SSEA-3, SSEA-4, Tra-1-60, and Tra-1-81, Rex-1 while mesenchymal stem cell markers, that is, CD73, CD90, and CD105 are showed up after some time, though unequipped for expressing hematopoietic or endothelial markers (i.e., CD14, CD34, and

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CD45)[31]. FSCs obtained from first-trimester human fetuses are able of survival, show a mature neuronal phenotype and becoming functional after transplantation[32]. FSCs apply paracrine trophic activities on host tissues (predominantly, immune, brain and gastrointestinal tissues) and can form several diffusible neurotrophic and growth factors.

Adult stem cells

They are mesodermal in origin, derived from the bone marrow of children and adults capable of self-regeneration and transformation into fat, cartilage, and stromal cells of the bone marrow[33,34]. The different sources for obtaining the stem cells incorporate fibroblasts[35,36]; somatic cells[37,38]; the peripheral blood mononuclear cells (PBMCs)[39]. Somatic cells provide the source for iPSC, for example, pancreatic beta-cells, liver[40], and keratinocytes[41]. However, in some cases, terminally differentiated cells, such as B-cell lymphocytes[42] and neurons[43] have also been utilized.

Adipose-derived MSCs

Adipose-derived mesenchymal stem cells (AD-MSCs) are getting popular regarding autologous cell therapy, capable of differentiating into mesenchymal lineage including adipogenic, osteogenic, chondrogenic variants. They can be obtained by methods like small volume lipo-aspirate[44].

Umbilical cord-derived MSCs

Among different sources of stem cells include both umbilical line and placenta[45]. Umbilical cord blood-derived mesenchymal stem cells are hematopoietic. The stroma of the cord is also a source of primitive stem cells dwelling in the Wharton's jelly (WJCs). WJCs delineate low levels of human leukocyte antigen (HLA)- ABC and no HLA-DR so ready to limiting the mouse splenocytes and human fringe blood lymphocytes[46]. WJCs act as trophic support to neighboring cell populations and conjointly hold immunomodulation properties[47]. Moreover, human cord blood mononuclear cells (CBMNCs) have also been transplanted successfully[20].

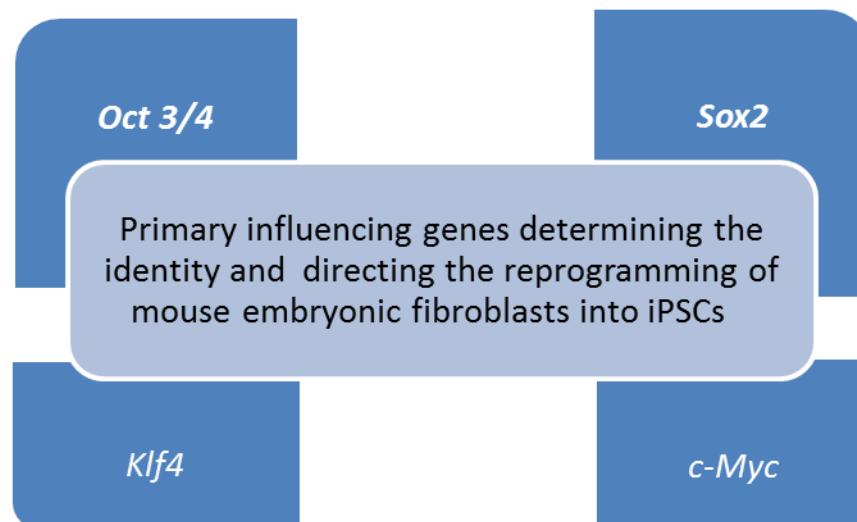*Citation: Muhammad Awais et al. Ijsrm.Human, 2020; Vol. 16 (3): 78-106.*

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Neural stem cells (NSCs)

Neural stem cells (NSCs) or neuroprogenitor cells (NPCs) are self-regenerating potential and differentiate into numerous cell types of central nervous system, can be gotten from both fetal and adult stem cells[48]. They can be inferred from viable human neurons and glial cells[49]; dental pulp cells[16]; from adult stem cells located in the lamina propria of olfactory epithelium hence named olfactory ecto-mesenchymal stem cells (OE-MSC)[50];

Properties of stem cells:

Genes expression

The change of one cell type to another is called *Transdifferentiation* whereas the process of reprogramming a cell type into a pluripotent state and then into the cell type of interest is called *reprogramming* [51]. The first impacting genes deciding the identity and coordinating the reprogramming of mouse embryonic fibroblasts into iPSCs incorporate Oct3/4, Sox2, Klf4, and c-Myc[52,53]. The resulting generation of mouse embryonic stem cells was indistinguishable to parent cells and showing pluripotent stem cell markers, SSEA-3, SSEA-4, Tra-1-60, and Tra-1-81. The association of comparable genes was also portrayed in human adult dermal fibroblasts to iPSC[52]. In another data, a slight distinctive factors Oct4, Sox2, Nanog and Lin28 were utilized in human fibroblast reprogramming[54].

Oct 3/4	Sox2
Primary influencing genes determining the identity and directing the reprogramming of mouse embryonic fibroblasts into iPSCs	
Klf4	c-Myc

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Several studies revealed transdifferentiation of human fibroblast into neurons[55,56]. Vierbuchen et al., inspired by the work of Yamanaka and Melton's groups, came up with 19 genes which were important in neural development or epigenetic modifications. These incorporate Brn2 (Pou3f2), Ascl1 and Myt1l transcription factors, determine the destiny of mouse embryonic stem cells and postnatal mouse fibroblasts into neurons[57]. Human dermal fibroblasts could also be transdifferentiated into neurons by the impact of NeuroD1, a basic helix–loop–helix transcription factor in about 3 weeks.

DIFFERENT METHODS TO DERIVE NEURONS FROM SOMATIC CELLS

1-Somatic cells such as skin fibroblasts can be reprogrammed to become iPSC and then differentiated into neurons and glia

2-Somatic cells can also be transdifferentiated to become induced neural stem cells (iNSC),

3-Somatic cells directly transdifferentiated to become induced neurons (iN)

Transdifferentiation of fibroblasts straightforwardly into neural stem cells (NSC) includes several transcription factors[58–62]. It was illustrated that fibroblasts could turn into NSCs by regulating Sox2 alone and also delineated the effect of Oct4, Sox2, Klf4, and c-Myc[59].

Differentiation pattern and guidance:

Stem cells can generate a three-dimensional structure of an organ i.e., laminar structure of the brain that model the developmental staging. Pluripotent stem cells, when permitted to develop in culture, will shape neurospheres in a three-dimensional design mirroring the layers of the cortex. Migration of N-cadherin+ neural progenitors towards Sox1+ outer regions and afterward these cells slowly move inward. On cut section, immunofluorescent staining uncovers Reelin+ and Tbr1+/Reelin−/Bf1+ neurons on days 7 and 8, whereas Ctip2+/ Emx1+ neurons were shown on and after day 10. Brn2+/Bf1+ cells were present during days 10–13. These Brn2+ neurons

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moreover appear with other upper CP markers such as Cux1 and Satb2 [63]. Moreover, birth-date examination pulsing, BrdU during days 8-14 and analyzing the BrdU positive cells on day 16. The birth of Reelin+ (layer I), Tbr1+/Bf1+ (layer VI), Ctip2+ /Emx1+ (layer V), and Brn2+/Tuj1+ (layer II/III) neurons were present on days 8–10, 9 to 10, 10 to 11, and 12 to 13, respectively.
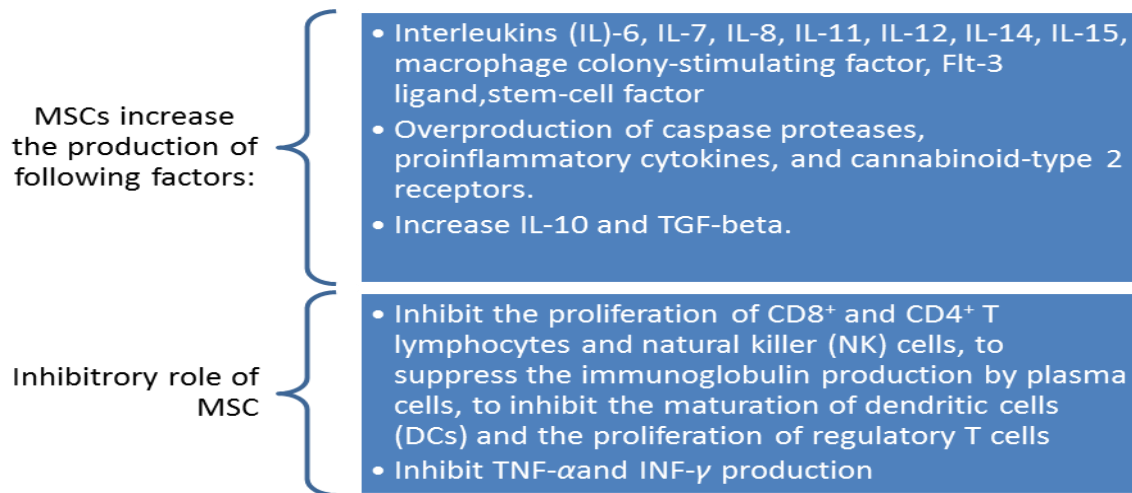
Embryonic stem cells (mESC) produce NSCs which pass through the normal stages of developmental and differentiate into neurons[64]. By uncovering mESC with a sonic hedgehog inhibitor, cyclopamine, progenitors gets differentiated to the dorsal cortical. On advance analyzing these pyramidal cells, markers of lower layer neurons appeared over time. Studying axonal projections of grafted ESC derived neurons by TAU (MAPT)-GFP knock-in ESC line, Gaspard et al. , after growing the TAU-GFP mESC for 12-17 days, the differentiated cells were transplanted into the frontal cortex of neonatal mice, showing the neurons exhibit axons which followed cortical efferents, uncovers that the neurons imitate cortical layer.
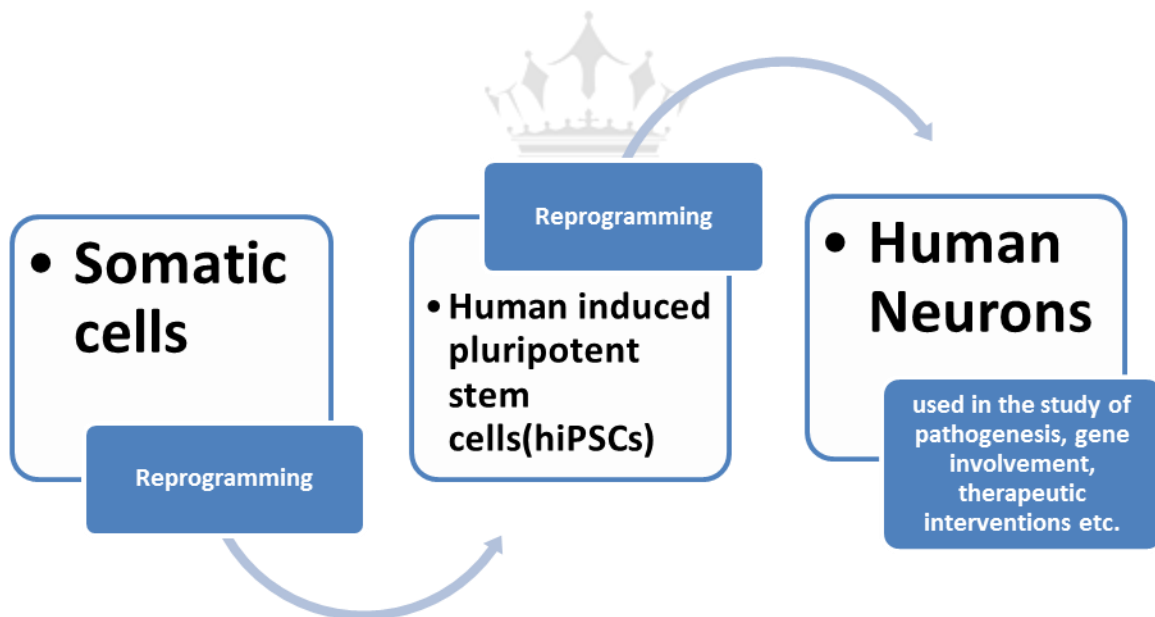
Immune-modulatory effects:

MSCs have shown the capacity to inhibit the immune system and enhance neurogenesis, in this way their application in therapeutics revealed likely outcomes in different settings including some clinical studies even[65]. This is due to the unique ability of MSCs i.e., migration to injury

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location and release of pro-inflammatory cytokines, subsequently smothering immune system and making themselves a successful transplantation modality in autologous as well as heterologous setting without requiring immunosuppressant drugs[66–69]. For this reason, genetic modification or pretreatment before transplantation is not recommended[70,71].

MSCs increase the production of following factors:
- Interleukins (IL)-6, IL-7, IL-8, IL-11, IL-12, IL-14, IL-15, macrophage colony-stimulating factor, Flt-3 ligand,stem-cell factor
- Overproduction of caspase proteases, proinflammatory cytokines, and cannabinoid-type 2 receptors.
- Increase IL-10 and TGF-beta.

Inhibitrory role of MSC
- Inhibit the proliferation of CD8+ and CD4+ T lymphocytes and natural killer (NK) cells, to suppress the immunoglobulin production by plasma cells, to inhibit the maturation of dendritic cells (DCs) and the proliferation of regulatory T cells
- Inhibit TNF-$\alpha$and INF-γ production

The paracrine functions of stem cells (i.e., the bio-pharmacy or the secretome) are picking up huge reputation[72,73]. Implanted stem cells utilize diverse mechanisms to cause their immunomodulatory effect including 1) cell-to-cell contact activation mechanism through which pro-inflammatory macrophages are changed into anti-inflammatory macrophages[74,75]; 2) paracrine secretome activity[76]. MSCs exert the plastic response in the host damaged tissue, synthesize and release survival-promoting growth factors as well as the synaptic transmitter by causing local re-innervation, integrate into existing neural and synaptic network, and establishing plasticity[77].

Variations in levels of TNF-αand INF-γ (decrease)and IL-10 (increase) levels inhibit T-cell recognition and expansion[78]. MSCs also able to change the NK cells through paracrine activity by producing PGE-2 and IL-10 which expert impact by changing T-cells responses[79], besides, by expressing tryptophan catabolizing enzyme indoleamine 2,3,-dioxygenase as well as Galectin-1[80,81]. MSCs also regulate immune response by the release of secrete immune inhibitory factors such as IL-10 and TGF-b without modifying the process of antigen presentation to T cells[82,83].

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It is not the culture time of MSCs to permit them picking up immunosuppressive capability and accomplishing the functional maturation to initiate allogeneic T cell apoptosis, when compared to freshly isolated, irradiated MSCs [84].

Safety:

Administration of $1–2.2 \times 106$ cells/kg of MSCs have caused no adverse effects while considering bone marrow cell transplantation[85]. Although further studies can uncover the real destiny concerning the safety of engrafting stem cells.

.Route of delivery:

Stem cells can be transplanted through various routes including injection into the lateral ventricle [86]; intramuscular approach[19]; intranasal administration[19]; intrathecal approach[19]; intravenous administration[20].

Pathogenesis (Possible mechanisms of ASD):

Alteration in neuronal structure:

Astroglial cells, or astrocytes, encompass different parts of the cerebral endothelium and assume an essential job in directing perfusion[88] and blood-brain barrier function[89]. Neurons derived from iPSCs of the unhealthy patient indicated a diminished number of neural connections and reduction in soma size, altered density of spine and electrophysiological absconds involving calcium signaling[35]. Synaptic deficits in ASD are directed by genes controlling protein synthesis, receptor development, and post-synaptic scaffold architecture design[90].

Astrocyte dysregulation (i.e., neuronal development inconsistency, variety in size and number of microglia) is associated with the pathophysiology of ASD[65,91]. Indeed, ASD subjects demonstrate a diminished number of Purkinje cells in the cerebellum[92]. These changes could reflect deficient cortical organization in ASDs development. Furthermore, autism is related to dysregulation in the development and plasticity of dendritic spine morphology[93]. In autism,

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excitatory and inhibitory cortical neurons add to minicolumn structure abnormalities and functional imbalance in cortex[48].

By synchronous and controlled formation of late cortical progenitors (LCPs) differentiating into glutamatergic cortical neurons of upper layers by iPSCs empower us to study the ability of LCPs in various periods of growth and associated molecular modifications included. The decline in time of differentiation of these progenitor cells into neurons provide a realistic chance to ponder on postmitotic neurons from these LCPs and response of various molecules affecting extension and branching of neurites[94]. The cellular level investigation of glutamatergic synapse arrangement, capacity, and maintenance by iPCSs modeling have empowered us to know the neuronal and synaptic development process in cells[95].

Breaking down of GABAergic neurons and therefore inhibitory signals result in the inability to direct the neuronal circuit engaged with ASD. By utilizing combinatorial and transient tweak of developmentally relevant dorsoventral and rostrocaudal signaling pathways (SHH, Wnt, and FGF8), we proficiently produced medial ganglionic eminence (MGE) cells from iPSCs. Secretion of various molecules originated by adjacent sources and moving to target locales help to coordinate the differentiation of GABAergic interneuron progenitors emerging from (MGE) versus caudal ganglionic eminence (CGE) by FGF8/FGF19 signaling pathway.Lhx6- expressing GABAergic interneurons produce from human MGE cells. By tweaking the signs may help in the healthy growth of GABAergic interneurons[96]. Cortical GABAergic interneurons regulate cortical excitation, and their brokenness is embroiled in a multitude of neuropsychiatric disorders[97].

Genetic mutations:

iPSCs give us a chance to uncover the conceivable role of genetic variations in the ASD patient and their products engaged with the arrangement of the unique feature of the human brain. It additionally settles the question of separation of undifferentiated stem cells into various pathways extending from general to particular ones and into various cells at influenced sites (e.g., neurons, cardiomyocytes, hepatocytes, and myocytes)[38]. Advancements of gene-editing innovations on iPSCs are empowering new methodologies for enlightening the pathogenic

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explanation of human diseases[98]. We can investigate distinctive disease markers and profile the diverse scope of gene expression[99].
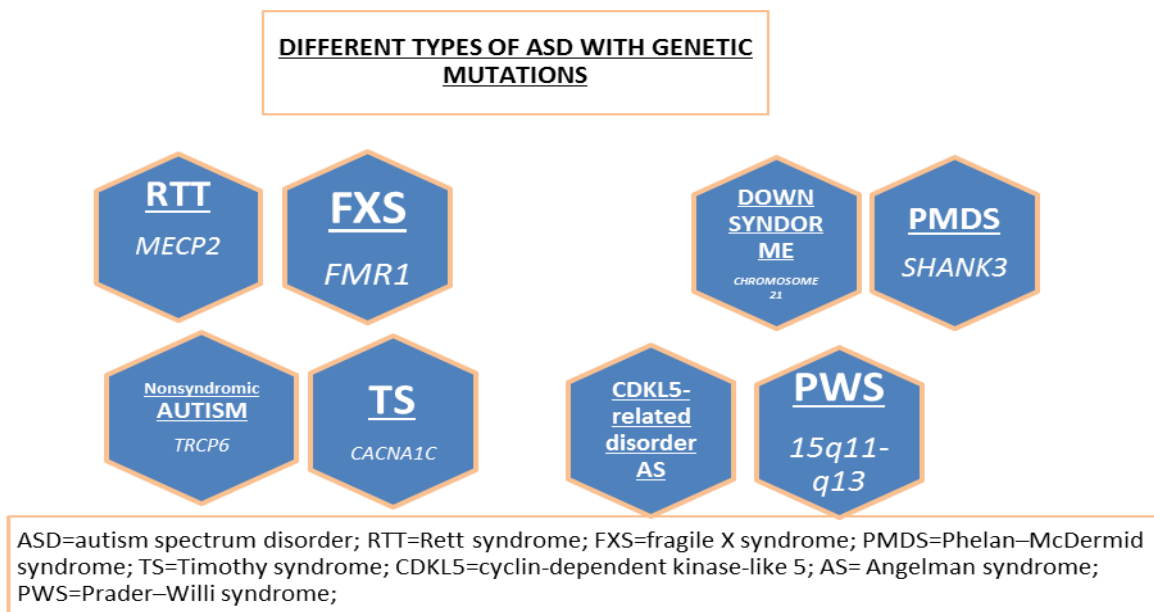
An examination report a de novo balanced translocation disturbance of TRPC6 (a cation channel), TRPC6 decrease or haploinsufficiency prompts changed neuronal improvement, morphology and working and impact of methyl CpG binding protein-2 (MeCP2) levels on TRPC6 articulation (transformations in MeCP2 uncovering normal pathways among RTT disorder) in a non-syndromic autistic person. Genetic sequencing of TRPC6 in 1041 ASD people and 2872 controls uncovered fundamentally more nonsynonymous changes in the ASD populace. Without further ado, that TRPC6 is a predisposing gene for ASD that may demonstrate in a multiple-hit model[16].

Transient receptor potential canonical 6 (TRPC6) signaling pathways
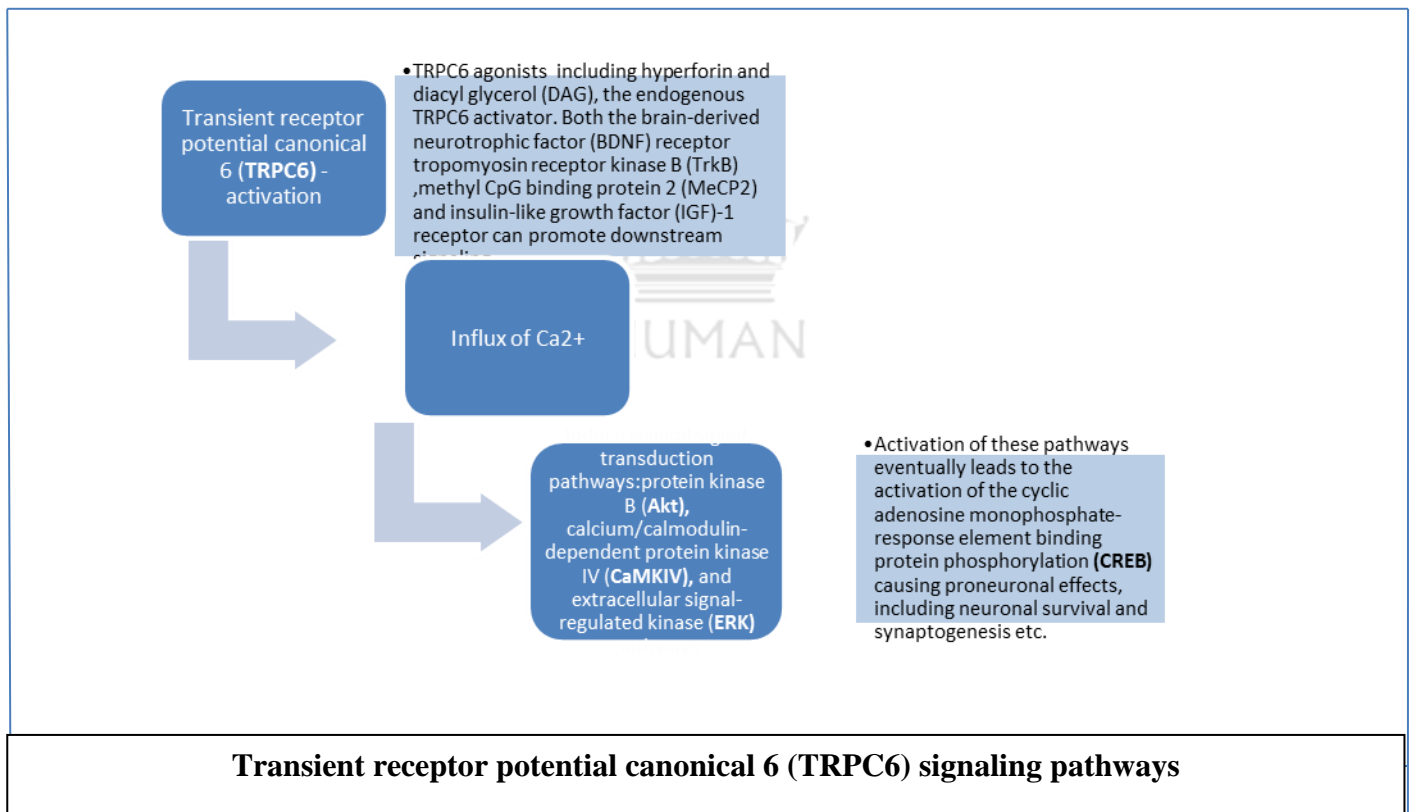
Chromodomain helicase DNA-binding protein 8 (CHD8) inadequacy assume an immediate impact in neuronal development and ASD hazard. (CHD8) which codes for an individual from the CHD group of ATP-dependent chromatin-remodeling factors. De novo loss-of-function mutations were recognized in 12 people with results in adjusted articulation of 1715 genes,

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including both protein-coding and noncoding ASD and zero controls. Little meddling RNA-mediated knockdown of CHD8 in human neural progenitor cells taken after by RNA sequencing uncovered that CHD8 insufficiency RNAs. Among the 10 most changed transcripts, 4 (40%) were noncoding RNAs. The transcriptional alterations among protein-coding gene included a very interconnected system of genes that are more influencing in neuronal growth and in beforehand recognized ASD competitor qualities[11].

RNA-seq investigation did on iPSCs that were heterozygous for CHD8 knockout (KO) alleles created utilizing CRISPR-Cas9 gene editing.TCF4 quality articulation was, once more, altogether upregulated. Pathway investigation completed on differentially expressed genes (DEGs) uncovered an advancement of genes associated with neurogenesis, neuronal differentiation, forebrain growth, Wnt/β-catenin signaling, and axonal guidance, like our past examination on NPCs and monolayer neurons. There was additionally huge cover in our CHD8+/ - DEGs with those found in a transcriptome investigation. Surprisingly, the best DEG in the analysis was the non-coding RNA DLX6-AS1, which was uniquely upregulated in both studies; DLX6-AS1 managed the expression of members of the DLX (distal-less homeobox) gene family and was likewise upregulated. DLX genes code for interpretation factors that assume a crucial job in GABAergic interneuron differentiation[100].

DIFFERENT TYPES OF ASD WITH GENETIC MUTATIONS

RTT — MECP2
FXS — FMR1
DOWN SYNDORME — CHROMOSOME 21
PMDS — SHANK3
Nonsyndromic AUTISM — TRCP6
TS — CACNA1C
CDKL5-related disorder AS
PWS — 15q11-q13

ASD=autism spectrum disorder; RTT=Rett syndrome; FXS=fragile X syndrome; PMDS=Phelan–McDermid syndrome; TS=Timothy syndrome; CDKL5=cyclin-dependent kinase-like 5; AS= Angelman syndrome; PWS=Prader–Willi syndrome;

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Interruption of a particular gene, GTDC1 utilizing long- insert DNA paired-end tag (DNA-PET) sequencing approach, in wild kind human neural progenitor cells (NPCs) and neurons portrayed a comparative phenotype as patient's iPSCs[101]; clustered regularly interspersed short palindromic repeat-associated protein 9 (CRISPR/Cas9) method for genome altering in 3D organoid frameworks has been utilized to analyze transformations that reason autism[102] and in the disease modeling field[103]. In an alternate report, hESC were produced with the trinucleotide expansion recognized by preimplantation genetic diagnosis. The ESC showed FMR1, and the promoter was unmethylated. Notwithstanding, the FMR1 promoter gets methylated upon differentiation and causing a decrement of FMR1 protein[104]. Curiously, two other groups utilized somatic cells with the trinucleotide expansion to iPSC. Their finding suggested methylation of FMR1 promoter leading to an inhibitory effect on FMR1 expression[15]. The promoter of FMR1 becomes methylated due to the trinucleotide repeat and is resistant to the reprogramming process.

Immune hyperactivity in autism:

Astrocyte physiologically beat disease by producing inflammatory cytokines, for example, TNF-alpha, IL-1beta, and IL-6 [105] and also different chemokines, for example, CXCL10, CCL2, and BAFF regulate adaptive immunity[106]. Autism people indicate diminish levels of inflammatory cytokines, for example, IL-10[107] and TGF-beta[108], subsequently building up a hyperactivity of immune state[16]. ELISA of CSF samples of ASD patients reveals overproduction of inflammatory cytokines[109]. Plasma level of INF-gamma is additionally discovered brought up in ASD people [106]. T cells and B cells anomalies have likewise been found in the autism individuals comprising of systemic T cell lymphopenia, altered cytokines formation and variable reactions to mitogens[110]. Studies have indicated a change in regulation of the immune system mainly CD3+, CD4+, and CD8+ T cells, and additionally in NK cells in ASD patients. The excess generation of IL-1β by peripheral blood mononuclear cells (PBMCs) have also been reported[111].

In autism individual, a few kinds of autoantibodies have discovered clarifying the immune system nature of illness when contrasted with controls, including antibodies to myelin essential protein, brain extracts[112,113], Purkinje cells and gliadin extracted peptides[114], neuron-axon filament, glial fibrillary acidic protein, and neutrophic factors[115]. Another viewpoint incorporates the high pervasiveness of immune system ailments in relatives of autism individuals[116].

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Autoimmunity is related with both HLA haplotypes and also complement component gene polymorphisms[117].

Hypoperfusion of brain in autism:

Youngsters with autism have been reliably appeared to have distorted, or subnormal CNS blood flows and also coming about hypoxia. Deformities incorporate basal hypoperfusion and diminished perfusion in response to stimuli that under typical conditions upregulates perfusion. In autism, the related hypoxia is not overwhelmingly apoptotic or necrotic to neurons however connected with malfunctioning[118]. Hypoperfusion may add to abandons by causing hypoxia as well as taking into consideration anomalous metabolite or neurotransmitter aggregation. This is one reason why glutamate toxicity has been embroiled in autism[119] and a clinical trial at turning around this utilizing the inhibitor of glutamate toxicity, Riluzole, is as of now in advance. Different causes incorporate the oxidative stress and inflammatory processes and impact of ecological factors, therefore, helping the utilization of pharmaceuticals and stem cells as a conceivable contender for the treatment of (ASD)[120].

THERAPEUTICS:

Drug screening

iPSCs give great chance to get to the human neurons(late cortical progenitors /LCPs and cortical neurons of the upper layers), and astrocytes[9,94], the headway in understanding the example of fundamental cell processes, genetic variability coding the neural tissue development has advanced the field of designing useful pharmacological and remedial interventions[37]. This includes the capacity to frame humanized illness display for the use of novel biogenic compounds influencing the ailment phenotype, focusing on the genetic changes and building up various cell substitution strategies[36]. A noticeable change appeared in the phenotypes of ASD people by use of insulin-like development factor-1 or TRPC6-particular agonist (hyperforin) and TRPC6 complementation[16,121].

Investigation of basic functional units, i.e. synapses through iPSCs inferred framework uncovers the procedure of arrangement and working of glutamatergic synapses and deciding the illness

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pathologies for the better understanding of shared processes and revelation of conceivable interventions. The impact of IL-6 on mental health and social changes contemplated on iPSCs human cell-based models unveil the pathogenesis of maternal immune activation (MIA) and role of luteolin-a natural flavonoid found in eatable plants-could avoid MIA-mediated abnormalities. The neural tissue from human induced pluripotent stem cells (hiPSCs) got from embryoid body-like aggregates were presented to IL-6 (100ng/ml) for 24h at day 51.IL-6 exposures caused the structural changes, i.e. expanded the area ratio of astrocytes (GFAP-positive area ratio) and diminished the area ratio of early-conceived neurons (TBR1-positive or CTIP2-positive region proportion) and additionally hoisted levels of phosphorylated STAT3, these progressions can be counteracted by Luteolin[122].

Trails on different medications are under scrutiny with variable outcomes. Usage of pioglitazone (PPAR-gamma agonist) in 25 youngsters came about 75% change accordingly on aberrant behavior checklist[17]. Psycho-stimulants, alpha-2 agonists, beta blockers, lithium, anticonvulsants, selective serotonin reuptake inhibitors, atypical antipsychotics, antidepressants, and mood stabilizers, are medications generally endorsed for significant help in ASD people, however, can't give cure [6,7]. Catatonia is treated with lorazepam and electroconvulsive therapy [8].

Stem cell transplantation

MSC can tweak a hyperactive immune system and elevate neurogenesis to make therapeutic potentials[65]. The expansion of CRISPR/Cas9 genome altering gives incredible potential to customized cell replacement treatment with hereditarily redressed hiPSCs[123].

Twenty-two kids with the pervasive developmental disorder were infused with human neural progenitor cells (hNPCs) into lateral ventricle, incorporating 13 youngsters with Rett disorder and 9 kids with autism; 17 patients, incorporating 8 patients with autism and 9 patients with Rett disorder, variable improvement. Autism Behavior Checklist before the operation, at one and six months post operation and after one year uncovered social communication scores were altogether diminished at a half year after transplantation and aggregate scores and communication and language scores were likewise radically lessened 1 year after transplantation (P<0.05) [18]. 71 youngsters with a serious neurological issue, (for example, autism, Rett Syndrome, giant axonal

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neuropathy) were directed intrathecally and intramuscularly infusion of bone marrow-determined mononuclear cells. 88% cases indicated a variable level of improvement[19].

In an alternate analysis, subjects were assessed prior and then afterward (6 and 12 months) organization of intravenously and subcutaneously fetal stem cells. The Autism Treatment Evaluation Checklist (ATEC) test and Aberrant Behavior Checklist (ABC) scores demonstrate noteworthy contrasts ($p < 0.05$) for the spaces of social interaction, sensory, and generally speaking wellbeing, and decreases in the aggregate scores when contrasted with pretreatment values[124]. Diverse information from the small pilot study including ten patients, who were taken after 3, 6, 12 or 24 months after the organization of stem cells. They were gotten to utilizing ISAA and WeeFIM scales indicating notable improvement[2].

Another investigation including 37 subjects determined to have an autism with arrangement of three groups: 1) combined transplantation of human cord blood mononuclear cells /CBMNC group (14 subjects, got CBMNC transplantation and restoration therapy); 2) Combination group (9 subjects, got both CBMNC and umbilical cord-derived mesenchymal stem cells (UCMSCs) transplantation and recovery treatment), and 3) Control group (14 subjects, got just recovery treatment). They were administered weekly stem cells intravenously and intrathecally. They were gotten to utilizing the Childhood Autism Rating Scale (CARS), Clinical Global Impression (CGI) scale and Aberrant Behavior Checklist (ABC) when treatment indicating unusual distinction 24 weeks post-treatment. Transplantation of CBMNCs indicated adequacy contrasted with the control group; be that as it may, the mix of CBMNCs and UCMSCs delineated more significant remedial impacts than the CBMNC transplantation alone[20]. In another setting, an experiment about utilizing a mixture of MSC and cord blood CD34+cells has demonstrated an enhanced response in autistic kids[125].

iPSCs transplantation can be made more profitable by setting up various assays with demonstrated efficacy to psychiatric disease pathophysiology, capably making and supporting specific neural cell types concerning provincial character is concerned, data reproducibility across over labs. Moreover, different proposals can be useful, including :(a) empowering the replication of results by systematizing conventions and tests used transversely over laboratories;(b) upgrading development by creating more affordable/speedier concentrating on

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techniques, scientists and measures; and (c) improving resource sharing and participation, with a highlight on brisk sharing of new cell lines, advances, and best practices, possibly melded into an open private organization[126].

Ethical issues:

When, the more understandings regarding the job of iPSCs in ASD, the more discussions in autism research have been raised with the advancement of autism-specific iPSC biobanks demonstrate a real necessity for authorities to doubtlessly pass on the confinements and potential results of iPSC research to ensure the research participants can give informed and valid consent[127]. Data about these studies vary in quality, making unusual conditions for parent's fundamental choice for a child's care. Moreover jumbling this scene are centers that promote these intercessions as an honest to goodness treatment for a cost. The general population who considered taking their child with ASD abroad for iPSCs transplantation on the premise of their usage of different wellsprings of stem cell-related health data information and their level of trust in these sources. Members uncovered that while the Internet was their most endless wellspring of information, it was not all around trusted. Alternatively, on the other hand, possibly, information sources trusted in most were examiners and the science journals in which they convey diverse guardians of children with ASD, and therapeutic administrations providers. These disclosures include a division between information searching for tendencies and information trusted in sources. A definitive helpfulness by utilizing iPSCs require more endeavors to build up the ultimate results in this field[128].

CONCLUSION

iPSCs are equipped for producing pluripotent cells that can separate the assortment of related cell types; this property is the premise of their use in the field of research for the diseases that can't be contemplated legitimately on alive subjects due to the constrained accessibility of source and modified explanations of results. By giving in vivo disease models to the investigation of such complex disorders including ASD, give a chance to better understanding the conceivable component of pathogenesis, hereditary impacts and testing remedial methodologies. Here, we depicted the role of these iPSCs was very promising by uncovering the hidden aspects of

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pathogenesis, i.e. changes in neural structure, genetic transformations, molecular variability, immune hyperactivity state, hypoperfusion of brain, oxidative pressure, environmental and natural variables. Remedial intercessions concerning drug screening and transplantation treatment in the various setting are likewise being tried comprehensively, to acquire practical advances in this field. By the iPSCs use in ASD, a promising future can be predicted. However, the rest of choice can be left on future analysts for advancing investigation in the field of research.

Disclosure Statement:

There is no conflict of interest in term of financial support or relationship.

Figure Legend:

All the figures has been pasted to the specific place in the article along with separate file (jgp.) and no description is needed separately.

Excess of Word Count

This review article have almost 5500 words excluding title page and references.

Author Contributions:

All authors who have contributed equally as a group to each of the key contributions i.e. conception and design of the study; acquisition and analysis of data; drafting the manuscript or figures: or others.

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