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Recent Advances in Research on Down Syndrome

Poulami Majumder, Pranami Bhaumik, Priyanka Ghosh,
Mandar Bhattacharya, Sujoy Ghosh and Subrata Kumar Dey

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Abstract

Down syndrome (DS) or trisomy 21 is one of the most important genetic causes of mental retardation. Sincere and significant attempts have been made towards understanding the congenital diseases that affect DS patients. Better understanding of gene networks associated with such malformations will help to predict the complex genetic trait behind congenital disease in DS and will also provide the basis for tailored gene therapies that could begin to heal or prevent such malformation without the need to resort to invasive surgery. Further, susceptible mutation screening in women will also be helpful for both prenatal diagnosis of DS birth and assessing the risk of predisposition to Alzheimer's disease and congenital heart disease. Stress condition and neurodegeneration are two important markers in Down syndrome patients and mtDNA variation can also be used as an important biomarker. It has been suggested that nutraceuticals which reduce reactive oxygen species (ROS) level may be used to treat trisomy 21 condition. As mitochondria play a crucial role in the regulation of free radicals, only a detail analysis will reveal the origin of phenotypic characteristics among trisomy 21 DS patients. On the other hand, several mechanisms are responsible for neurodegeneration as well as altered cognition. It includes impaired neurogenesis leading to hypocellularity in the cortex, hippocampus and cerebellum, altered dendritic morphology, altered synapses, increased inhibition and neurodegeneration. The new knowledge of the pathogenic mechanisms in DS individuals has been acquired from mouse model. These studies provide the basis for developing new drugs for clinical trials in DS individuals and to sustain the hope that some of these drugs will be useful in treating intellectual disability in DS individuals.

Keywords: Down syndrome, trisomy 21, congenital heart disease, Alzheimer's disease, mitochondria, mouse model

1. Introduction

Down syndrome (DS) or trisomy 21 is the most frequent live born chromosomal aneuploidy in humans characterized by an extra chromosome 21 [1]. Myriad researches have contributed significantly towards understanding the management and control of disorders associated with Down syndrome. Since middle of 19th century, Down syndrome research has progressed alongside and in response to more general scientific advances. These researches attempt to cover the etiology, treatment, management, control, and prevention of DS. Both *in vitro* and *in vivo* experiments are carried out to understand the molecular mechanism of the origin of this aneuploidy. Many exciting areas are currently being investigated in relation to DS. A number of genes have been identified, which are putative candidates for phenotypic abnormalities. Use of Down syndrome mouse model, which is segmental trisomies of homologous segment of human chromosome 21, has facilitated greatly the process of reverse genetic approach to explore the gene–protein relationship in Down syndrome. Extensive studies are carried out in areas involving psycho-somatic and neural control of functions such as learning, behavior, and foetal brain development.

The research on Down syndrome has progressed and it can be assumed that people with Down syndrome will enjoy better quality of life in future. The most prevalent disorders among Down syndrome patients that have attracted the attention of research community are Alzheimer's disease and congenital heart defect. To go deep into the problem and to understand the exact etiology of these disorders, several approaches have been taken. One among them is mouse models for segmental trisomies, which are being used for better understanding of these disease conditions. The ultimate goal of all research approaches is to contribute toward the better management of lifestyle of Down syndrome individuals.

2. Congenital Heart Disease (CHD) in Down Syndrome

Down Syndrome (DS) is characterized by a combination of multifaceted congenital abnormalities with various degrees of severity. Among them cardiac anomalies are found in nearly 50% of DS cases. Cardiac abnormalities in DS include mainly atrioventricular septal defect (AVSD), ventricular septal defects (VSD), atrial septal defect (ASD) and few percentages of isolated tetralogy of fallot (TOF) of which approximately 40–60% includes an atrioventricular septal defect (AVSD) [2]. The developmental basis of atrioventricular septal defect also known as an atrioventricular canal defect or endocardial cushion defect is complex. This congenital cardiac anomaly occurs when the superior and inferior endocardial cushions fail to close completely, resulting in incomplete formation of atrial and ventricular valves and septa. The tricuspid and mitral valves that normally separate the hearts upper and lower chambers are not formed as individual valves; instead, a single large valve is formed which does not close tightly. A large hole in the centre of the heart exists where the wall between the upper chambers join the wall between the lower chambers, allowing the blood to flow between all the chambers of the heart. This is called as a complete AVSD. In case of partial AVSD, there is usually a hole

in the wall between the atria or a hole in the wall between the ventricles near the middle of the heart, but there are usually two valves between the atria and ventricles and not a common valve as seen in complete AVSD. In partial AVSD, usually the mitral valve does not close completely and allows the blood to leak backward.

2.1. Recent studies on CHD

Higher incidence of congenital heart disease (CHD), especially AVSD, associated with DS has made the identification of CHD associated genes very challenging. Therefore, many researches focused on chromosome 21 (Ch21) genes, based on the hypothesis that overexpression of these genes may play a role in the etiology of AVSD in DS. Studies have implicated Ch21 genes, *COL6A1*, *COL6A2*, and *DSCAM* as potential contributors to heart defects in DS [3–5]. A recent study has shown that overexpression of *DSCAM* and *COL6A2* cooperatively causes atrial defects in mice [6]. Recently a candidate gene approach carried out among Down syndrome individuals with AVSD and Down syndrome without CHD suggests a potential contribution of VEGF-A, ciliome, hedgehog and folate pathway genes such as *MTHFR*, *MTRR*, *SLC19A1*, *MTR*, and *CBS* to the pathogenesis of CHD in DS [7–9].

Many studies based on the premise that myriad of genes are involved in cardiogenesis, and perturbation in any of this gene by mutation can cause CHD, therefore, highlighting the role of non-chromosome 21 gene mutation to play a key role in the etiology of AVSD in DS. For example, pathogenic mutations in the *CRELD1* gene have been found to be associated with AVSD [10]. Studies have also shown that how polymorphic haplotypes of *CRELD1* increase the risk of AVSD, and the susceptibility is exacerbated in DS, possibly due to the trisomy 21 genetic background [11]. Furthermore, there is a growing body of evidence, highlighting the role of epigenetic in the development of AVSD in DS [12].

There are multiple risk alleles that play an important role in the pathogenesis of congenital heart disease (CHD) in DS. Alone trisomy 21 background is not enough to reach the threshold needed for the development of CHD. There exists a multifactorial model where genetic and epigenetic variants, unknown environmental factors, and stochastic events are required in addition to trisomy 21 background to cross the threshold for developing CHD in DS.

3. Relationship between Alzheimer's Disease and Down Syndrome

Alzheimer's disease (AD) is well known as the major cause of dementia in elderly people, characterized mainly by cognitive decline and other motor dysfunction. Several lines of researches indicate that Alzheimer's disease share some common genetic factors with Down syndrome. Imaging techniques have confirmed AD-like pathogenic signs in the brain of most DS patients after 40 years of age [13, 14]. Frequent birth of babies with DS is evident in families with AD patients. Moreover, greater number of AD patients are counted among the relatives of DS. Neurons progressively and irreversibly die chiefly due to deposition of amyloid beta protein and eventually perturb neurosynaptic circuits in the brain [15]. The amyloid hypothesis states that APP (amyloid precursor protein) gene, located on chromosome 21, encodes for

amyloid precursor protein which is proteolyzed by enzymatic cascade and eventually produce amyloid beta protein that in turn oligomerizes and forms beta-plaque [16]. The increased amyloid load due to overexpression of APP in trisomy 21 cells is hypothesized to be a cause of AD in DS [17]. Moreover, APP gene mutations are also found in both AD and DS [18]. Apolipoprotein E (APOE) is one of the key genes involved in the manifestation in sporadic AD cases; epsilon 4 allele of this gene is reported to be associated with deterioration in cognitive ability in DS patients [19].

3.1. Theory of chromosomal missegregation

Scientists have pointed out that chromosomal segregation error may be the possible underlying molecular link between these two disorders [20, 21]. Abnormality in cell cycle regulation due to mutations in different genes involved in both sporadic and familial AD cases is also apparent [20, 22, 23]. According to this theory, AD patients bear mosaic aneuploid cells in central and peripheral nervous system which are susceptible to apoptosis [20]. Besides neurons and buccal cells, lymphocytes are also found to be trisomic for chromosome 21 [23–27]. Again, inflammatory responses induced by overexpression of IL-1 in trisomic microglia increase amyloid beta production [28].

3.2. Relationship between Alzheimer's Disease and mothers of Down Syndrome child

Researches revealed that women giving birth to Down syndrome (DS) babies at younger age are prone to have AD with aging [29]. Young mothers bearing DS offspring are also found to possess APOE epsilon 4 allele with a higher frequency [30]. Presenilin 1 (PSEN-1) is another important gene playing a role in AD pathogenesis. Trisomy 21 aneuploidy and chromosomal instability are evident in AD patients with mutation in PSEN-1 gene [20, 31]. Association of polymorphism of PSEN-1 gene (rs165932) is also established in young mother, giving birth to DS babies due to nondisjunction error in second meiotic division of oocyte [32]. It is postulated that accumulation of mosaic trisomy 21 cells in both somatic and germline tissue make those women prone to AD in their later life and also responsible for giving birth to DS child. Thus the theory of chromosomal missegregation offers us a new insight into the understanding the molecular mechanism that bridges Down syndrome with Alzheimer's disease.

3.3. Other common factors linking Alzheimer's Disease and Down Syndrome

3.3.1. Mitochondrial dysfunction

Mitochondrial dysfunction is associated with AD pathology [33]. Protein members of mitochondrial electron transport chain are found malfunctioning in Alzheimer's disease [34]. Diminished cytochrome oxidase activity reflecting improper functioning of mitochondria in AD patients is revealed by biochemical, histochemical, and immune-histochemical analysis [35]. Showing similarity with AD cases, dysregulation in mitochondria is evident in Down syndrome etiology [36]. Individuals with DS also exhibit reduced activity of several mitochondrial enzymes, including cytochrome oxidase [37]. Thus oxidative stress due to mitochondrial dysfunction is typical in both AD and DS.

3.3.2. Abnormal tau phosphorylation

Another very strong hallmark of AD is the presence of intra-neuronal neurofibrillary tangle made up of hyperphosphorylated tau protein. The neurotoxic effect of these tangles makes the neurons vulnerable to death. Researchers revealed that the abnormality in tau phosphorylation is seen both in AD and DS [38]. A kinase enzyme called “dual-specificity tyrosine phosphorylated and regulated kinase 1A” or DYRK1A phosphorylates tau protein. This gene is mapped in the Down syndrome critical region of chromosome 21, hence present in triple copies in DS patients, giving rise to enhanced production of DYRK1A [39]. Moreover, hippocampal, neocortical, and entorhinal-cortical neurons show increased DYRK1A immune-reactivity in both AD and DS patients [40].

3.3.3. Altered endocytic pathway activity

Altered endocytic pathway activity is another common phenomenon that bridges both disorders [41]. Neurons internalize and modify extracellular molecules from cell surface via endocytosis and relay signals for intracellular biosynthetic pathways to occur. Initial processing of APP and APOE proteins and cellular uptake of amyloid beta take place in the early endosomes. Bigger size of early endosomes was seen in AD brain, suggesting increased endocytic pathway activity [42, 43]. Several growth factors, cell surface receptors, and other plasma proteins can be erroneously degraded and processed by activated early endosome in neurons, exposing them in peril. Such improper endolysis of neuronal glucose transporter is found responsible in reduced uptake of glucose in AD brain [44, 45]. Strikingly, pyramidal neurons with enlarged early endosomes are also found in DS fetus at 28 weeks of gestation [41].

4. Mitochondrial DNA analysis in Down Syndrome patients

The double-stranded circular mammalian mtDNA molecule of 16.5 kb contains a single long noncoding region, a displacement loop (D loop) region, the promoters for transcription of both mtDNA strands and the origin of leading strand replication (O_H). The origin of lagging strand replication (O_L) is surrounded in a cluster of tRNA genes. mtDNA codes two rRNAs (12S and 16S rRNA), 13 mRNAs (ND1–6, ND4L, Cyt b, COI–III, ATP6, and ATP8), and 22 tRNAs (F, V, L1, I, M, W, D, K, G, R, H, S1, L2, T, P, E, S2, Y, C, N, A, and Q).

4.1. Why study mitochondria in Down Syndrome patients?

Mitochondria controls one of the most important biochemical pathways, oxidative phosphorylation (OXPHOS). A mild imbalance in mitochondrial function or a slight change in mitochondrial structural integrity might lead to a severe cellular oxidative damage and finally apoptosis. As Down syndrome is an AD-like disease condition, oxidative stress plays a key role in disease pathogenesis with inevitable involvement of mitochondria.

4.2. Structural and biochemical anomalies in mitochondria among Down Syndrome patients

Several mitochondrial anomalies have been reported in trisomy 21 patients over the years of research. Decreased levels of several mitochondrial enzymes such as monoamine oxidase, cytochrome oxidase, and isocitrate dehydrogenase have been observed in trisomy 21 patients [37]. At genetic level, downregulation of mitochondrial enzyme genes and upregulation of mitochondrial extracellular matrix protein genes have been found out by oligonucleotide microarray in Down syndrome fetus [46]. The level of another important enzyme, pyruvate dehydrogenase, is found to decrease in the brain of trisomy 16 mouse [47–49]. At structural level, heavy accumulation of microfilaments, tubules, and abnormally shaped mitochondria is reported in cerebellar neuron of trisomy 16 mice [50]. The 20 kD complex has also been found out to be downregulated [49]. Mitochondrial membrane potential in peripheral blood mononuclear cell (PBMC) is decreased among Down syndrome individuals, which indicates severe impairment of mitochondrial function [51].

4.3. mtDNA variations among Down Syndrome patients

mtDNA because of its close proximity to mitochondrial membrane might undergo severe changes due to reactive oxygen species (ROS). mtDNA contains hyper variable D-loop region (HDR) and semi-variable regulatory control region (RCR). This particular region is responsible for overall mtDNA transcription mechanism and any adverse change in this region hampers the overall transcriptional procedure. Several heteroplasmic mutations have been observed in Down syndrome brains which include G70A, C114T, C150T, G185A, and 309.1-3insC. Down syndrome lymphoblasts and control lymphoblast share the A73G variant while they more commonly have the 309.1inC, A357G, and 522–523delCA [52].

5. Mouse model

In recent years, mouse models are used as standard tool for *in vivo* study. It provides an insight into the normal functions and regulation of genes and how these are altered in disease and how they contribute to severity of this disease. Administration of certain drugs as well as information on drug action, efficacy, and side effects also can be evaluated by this animal model [53]. So mouse models are used to enhance our knowledge on human genes, their functions, interactions, and biochemistry. The most studied mouse model for DS is the Ts65Dn mouse which possesses an extra copy of the chromosome number 16. The distal segment of mouse chromosome 16 (MMU16) is homologous to nearly the entire long arm of human chromosome 21 (HSA21), and thus trisomic mouse models are developed in such a way that it genetically resembles human condition. Ts65Dn and Ts1Cje mice mimic many of the behavioral, learning, and developmental deficits characteristics in DS individuals [54–58]. The availability of sophisticated tools for mouse genetics and the conserved synteny between MMU16 and HSA21 have provided the basis for the development of many mouse models of DS. This similarity allows to test the critical region concept and to perform a genetic dissection of the complex DS phenotype.. The knowledge obtained from these models about the neuro-

biology of DS have yielded the development and analysis of several therapeutic strategies that could potentially be used to attenuate cognitive impairments in DS individuals. s

5.1. Recent studies on mouse model

Mouse modeling is a very useful technique to understand the neural mechanism underlying the cognitive impairment seen in Down syndrome. The association of Alzheimer's disease with Down syndrome and the regulation of involved genes are being investigated via mouse model [59]. DS individuals typically display an average Intelligence Quotient (IQ) of 50 (ranging from 30 to 70) and show an array of altered cognitive and behavioral phenotypes, including the incomplete and delayed acquisition of motor, linguistic, and visual-spatial abilities, impairments in learning and memory, and neurobehavioral disorders [60–62]. Holtzman et al. (1996) suggest that Ts65Dn mice are the most useful animal model to study the developmental and degenerative abnormalities in the DS brain *in vivo* [56]. Studies show that Ts65Dn mice mimic the specific age-related decrease in cholinergic function seen in Down syndrome and Alzheimer's disease [63]. The degeneration of cholinergic neurons in basal forebrain is age related and this finding raises the possibility that this model may be used further to understand mechanisms underlying selective neuronal vulnerability seen in DS and AD. Ts65Dn mice also carry a trisomy of MMU17 containing 60 genes nonhomologous to Hsa21, so this model does not have perfect construct validity [64]. Mouse modeling also revealed that the nerve growth factor (NGF) is required for the normal differentiation of basal forebrain cholinergic neurons (BFCNs) and the abnormalities in NGF levels or signaling in Ts65Dn mice may determine the regulating factors in neuronal degeneration [64]. GABA (gamma amino butyric acid) is an important neurotransmitter that regulates neuronal proliferation, migration, differentiation, and integration of newly generated neurons [65]. It has been suggested that upregulation of presynaptic GABA may be responsible for the increased hippocampal inhibitory postsynaptic potentials (IPSPs) observed in these mice [66]. Netzer et al. have tested the effect of β -amyloid reductions in the Ts65Dn mice which altered its phenotypes [67]. They administered the gamma secretase inhibitor DAPT (*N*-[*N*-(3,5-difluorophenacetyl)-*L*-alanyl]-*S*-phenylglycine *t*-butyl ester) into mice and this treatment reduced β -amyloid levels and rescued spatial learning in these mice. β -amyloid is a regulator of the glutamatergic system, and the authors proposed that the cognitive enhancing effects of DAPT could be mediated by an enhancement and/or a regulation of excitatory synaptic transmission. It has been proposed that pharmacological enhancements of the cholinergic system help to diminish the cognitive deterioration in DS with AD. Another research revealed that an acetylcholinesterase inhibitor, Donepezil, is widely prescribed to enhance cholinergic transmission to treat DS with dementia. However, the chronic administration of Donepezil did not improve learning and memory in Ts65Dn mice and causes ambiguous results in young adult individuals with DS [68]. Another drug named piracetam shows cognitive-enhancing effects in patients with a number of cognitive disorders and dementia and also in mouse models though the mechanisms underlying these effects are unknown [69]. However, piracetam treatment did not improve cognitive impairments in children with DS or in the Ts65Dn mouse [70].

The first partial trisomic models, the Ts65Dn and Ts1Cje models, demonstrated that DS phenotypes could be recapitulated in mice. More recently, knock-out and transgenic mice are developed in different laboratories for particular genes, though there is no mouse model that perfectly mimics a human condition. In the last 20 years, mouse models, particularly the Ts65Dn mouse, have been widely used to understand the neurobiological basis of intellectual disability.

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Author details

Poulami Majumder¹, Pranami Bhaumik¹, Priyanka Ghosh¹, Mandar Bhattacharya¹, Sujoy Ghosh² and Subrata Kumar Dey^{1*}

*Address all correspondence to: subratadey184@gmail.com

1 Department of Biotechnology, West Bengal University of Technology, Salt Lake, Sector I, Kolkata, West Bengal, India

2 Department of Zoology, University of Calcutta, Ballygunge Science College Campus, Kolkata, West Bengal, India

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