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Review article

Down syndrome: Neurobiological alterations and therapeutic targets

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ABSTRACT

Down syndrome (DS) is a genetic disease that occurs due to an aneuploidy of human chromosome 21. Trisomy of chromosome 21 is a primary genetic cause of developmental abnormalities leading to cognitive and learning deficits. Impairments in GABAergic transmission, noradrenergic neuronal loss, anomalous glutamatergic transmission and *N*-methyl-D-aspartate receptor signalling, mitochondrial dysfunction, increased oxidative stress and inflammation, differentially expressed microRNAs, increased expression of crucial chromosome 21 genes, and DNA hyper-methylation and hyperactive homocysteine trans-sulfuration pathway, are common incongruities that have been reported in DS and might contribute to cognitive impairment and intellectual disability. This review provides an update on metabolic and neurobiological alterations in DS. It also provides an overview of the currently available pharmacological therapies that may influence and/or reverse these alterations in DS.

1. Introduction

Down syndrome (DS) is a genetic disorder that develops as a consequence of an aneuploidy of human chromosome 21 (Hsa21) (Antonarakis et al., 2004; Letourneau et al., 2014; Opitz and Gilbert-Barness, 1990; Ruparelia et al., 2010). The most frequent form of DS is a result of full Hsa21 trisomy, which is an outcome of the inability of Hsa21 to segregate during meiosis in a developing ovum or, to a lesser extent, in sperm, culminating in an extra copy of the entire Hsa21 in all cell types. The mosaic form is rare and occurs in 3–4% of DS population, in which some cells within a single tissue type exhibit a normal karyotype while others exhibit a Hsa21 trisomy (Antonarakis, 2017; Asim et al., 2015; Rachidi and Lopes, 2008; Reeves et al., 2001; Sherman et al., 2007). The occurrence of partial Hsa21 trisomy leading to DS phenotype is extremely rare (Pelleri et al., 2016).

The incidence of DS is estimated to be 1/750–800 live new-borns, but the risk of Hsa21 non-disjunction increases with advanced maternal age (Loane et al., 2013; McKenzie et al., 2016; Rudolf et al., 2017). Differences in the use of prenatal screening and pregnancy termination have led to a wide variation in live birth prevalence between countries (Morice et al., 2008; Rudolf et al., 2017). A recent epidemiological study on the prevalence of major birth defects in the live birth

Abbreviations: Aβ, beta-amyloid; AD, Alzheimer's disease; AMPK, 5′ AMP-activated protein kinase; APP, amyloid precursor protein; BAX, BCL2-Associated X Protein; CAT, catalase; CBS, cystathionine beta-synthase; CNS, central nervous system; CoQ10, Coenzyme Q10; Drp1, dynamin-related protein 1; DS, Down syndrome; DSCR, Down syndrome critical region; DYRK1A, dual-specificity tyrosine (Y)-phosphorylation regulated kinase 1A; EGCG, epigallocatechin-3-gallate; GABA, γ-aminobutyric acid; GIs, γ-secretase inhibitors; GPCR, G-protein coupled receptor; GPX, glutathione peroxidase; Hsa21, human chromosome 21; iPSCs, induced pluripotent stem cells; LTD, long-term depression; LTP, long-term potentiation; Mecp2, methyl-CpG binding protein 2; miRNAs, microRNAs; Mnf2, mitofusin 2; MRC, mitochondrial respiratory chain; mTOR, mammalian target of rapamycin; NAM, negative allosteric modulator; NFAT, nuclear factor of activated T-cells; NKCC1, Na-K-clcotransporter 1; NMDA, *N*-methyl-D- aspartate; NPCs, neural progenitor cells; NRIP1, nuclear receptor interacting protein 1; Opa1, optic atrophy 1; PKA, protein kinase; APiB, C-labeled Pittsburgh compound B; RCAN1, regulator of calcineurin 1; RIP140, receptor-interacting protein 140; ROS, reactive oxygen species; SOD, superoxide dismutase; TSP-1, thrombospondin 1

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