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Review article

Disturbance of redox homeostasis in Down Syndrome: Role of iron dysmetabolism☆

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ABSTRACT

Down Syndrome (DS) is the most common genetic form of intellectual disability that leads in the majority of cases to development of early-onset Alzheimer-like dementia (AD). The neuropathology of DS has several common features with AD including alteration of redox homeostasis, mitochondrial deficits, and inflammation among others. Interestingly, some of the genes encoded by chromosome 21 are responsible of increased oxidative stress (OS) conditions that are further exacerbated by decreased antioxidant defense. Previous studies from our groups showed that accumulation of oxidative damage is an early event in DS neurodegeneration and that oxidative modifications of selected proteins affects the integrity of the protein degradative systems, antioxidant response, neuronal integrity and energy metabolism.

In particular, the current review elaborates recent findings demonstrating the accumulation of oxidative damage in DS and we focus attention on specific deregulation of iron metabolism, which affects both the central nervous system and the periphery. Iron dysmetabolism is a well-recognized factor that contributes to neurodegeneration; thus we opine that better understanding how and to what extent the concerted loss of iron dyshomeostasis and increased OS occur in DS could provide novel insights for the development of therapeutic strategies for the treatment of Alzheimer-like dementia.

1. Alzheimer-like dementia in Down Syndrome population

Down Syndrome (DS) is a congenital birth defect that arises by the complete or partial trisomy of Chr21 (trisomy21) and is the most prevailing genetic cause of intellectual disability with an incidence of around 1:800 births. The complete triplication of the entire Chr21 is not necessary to produce the clinical phenotype of DS individuals; indeed, the triplication of just a portion of the distal long arm, described as DS critical region (DSCR), has been identified as sufficient for this purpose [1]. The majority (95%) of DS cases are caused by non-disjunction of chromosome in meiosis I, during the formation of gametes; while 3.2% and 1.8% of residual DS cases are caused, respectively, by translocation and mosaicism [2].

The effects of trisomy 21 vary widely from one individual to the other and not every DS subject show all the phenotypic features caused by trisomy. Therefore, it is conceivable to separate DS features in two types: i) those seen in all patients, for example cognitive decline or facial dysmorphology; and ii) those that have variable penetrance, such as the congenital heart defect that is observed in 40% of DS cases.

In addition to the chromosomal abnormality, it is believed that additional environmental factors could to play an important role in determining different phenotypes. The “gene dosage hypothesis” proposes that the overexpression of trisomic genes and their encoded proteins is directly responsible for the different phenotypical alterations in DS [3,4]. The “amplified developmental instability hypothesis” postulates that the presence of multiple phenotypes is caused by the effects of the overexpression of trisomic genes on dysomic genes leading to an imbalance in their expression [5]. So far, results obtained by the analysis of DS cases and the development of DS mouse models support both hypotheses. Therefore, the combination of these two hypothesis indicates a complex scenario in which the consistently over- or down-expression of a subset of dosage-sensitive genes lead to different phenotypic features.

The main pathological features include seizures, leukemia, vision

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problems, thyroid dysfunction, diabetes and dementia, specifically early onset Alzheimer disease (AD) (reviewed in [4]).

In the last decade, DS neuropathology has become an attractive field of research for a number of reasons: i) DS can be regarded as a human model of accelerated aging; ii) DS allows correlation between genetic defects and pathological phenotypes; iii) and DS neuropathology correlates with neurogenesis defects, brain development abnormalities and cognitive impairment.

Some of the most consistent and significant alterations in DS involve the brain, which demonstrates reduced neuronal content, reduced frontal lobe volume and narrowed superior temporal gyrus. DS individuals, after the age of 40, develop a type of dementia that is similar to AD, the most common cause of dementia in the elderly population, with deposition of senile plaques containing amyloid beta-peptide (Aβ), neurofibrillary tangles (NFTs) composed of hyperphoshorylated tau, and cholinergic and serotonergic reduction [6,7]. The neurodegenerative process in DS population can be considered a “human model” of pre-clinical, early AD and could contribute to understanding the pathological mechanisms involved in the progression to late stage AD. The deposition of Aβ plaques and NTFs are the most prominent and detrimental neuropathological changes in AD brain and occur in cortical regions that are important in acquiring, storing and retrieving information. These regions include temporal lobe structures, such as the hippocampus, as well as frontal and parietal regions.

Characteristic features in AD brain are weakening of synaptic networks, neuronal loss and increase of brain atrophy [8,9]. Aβ and tau lesions affect several brain regions in DS, including prefrontal cortex, hippocampus, basal ganglia, thalamus, hypothalamus and midbrain and are believed to underlie the development of cognitive decline and dementia. However, although the depositions of Aβ plaques have been observed in fetus and young DS individuals [10–12], signs of dementia are clearly manifested many years later.

Interestingly, a recent study demonstrated elevated amyloid levels that does not reach a plateau in the nondemented DS population. The rate of amyloid accumulation differs by pre-existing amyloid burden and precedes atrophy or dementia in the DS population, similar to general AD progression, thus suggesting consistency of the AD pathophysiologic process in DS as well as in the general population [13].

The identification and characterization of the genes and proteins encoded on Chr21 is crucial to understand the mechanisms by which the chromosomal abnormality could contribute to the development of AD in DS individuals as well as in the general population. The entire sequence of human Chr21 is now known and there are 233 coding genes, 299 long non-coding genes (Ensembl release 78) and 29 microRNAs (miRBase release 21) [14]. After investigation with Swiss-Prot and analysis with Gene Ontology Annotation, the 207 proteins found encoded on Chr 21: i) take part in 87 different biological processes, and 11 proteins are involved in signal transduction; ii) have 81 different molecular functions among which DNA binding and transcription factor activity are the most prevalent with 15 proteins; iii) are localized in 26 different cellular components, nucleus and the plasma membrane with 19 and 15 proteins, respectively, are the most predominant cellular localizations [4].

2. Oxidative stress in Down Syndrome

Among putative mechanisms that contribute to the accelerated aging, cognitive and neuronal dysfunction in DS, the oxidative stress (OS) hypothesis has been recognized to affect neurogenesis and differentiation, connection and survival in the brain [6,15–17]. Increased OS has been implicated in the development and progression of neurodegenerative diseases and several studies confirmed the accumulation of oxidative damage in the brains of both AD and DS subjects [18–20].

OS is a condition that results from either overproduction of reactive oxygen and nitrogen species (ROS (Reactive Oxygen Species)/RNS), or by decreased antioxidant response. The presence of elevated fatty acids content in the nervous tissue, together with the high aerobic metabolic activity, are responsible of the brain susceptibility to undergo oxidative damage [21–23]. Accordingly, a strong correlation between higher OS levels and several cellular toxic processes in neurodegenerative conditions has been reported. ROS such as superoxide anion ($O_2^{-\bullet}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($HO^{\bullet}$), are generated as by-products of aerobic respiration and various other catabolic and anabolic processes [24]. The major source of free radicals is the mitochondrial oxidative phosphorylation pathway, in which electron leakage from the electron transport chain causes the formation of $O_2^{-\bullet}$ that, in turn, is converted by mitochondrial-resident MnSOD into H_2O_2 and O_2 [25]. Indeed, dysfnction of complex I has been demonstrated to be one of the major responsible of overproduction of ROS in skin DS fibroblast isolated from both fetal and adult subjects [26].

In the cytosol, H_2O_2 can be efficiently removed by antioxidant systems such as catalase (CAT), glutathione peroxidase (GPX) and thioredoxin peroxidase.

Interestingly, triplication of several Hsa21 genes such as *SOD1, APP, BACH1, Ets2, CR, S100β* among others are believed to be involved in the increased OS levels found in DS individuals and in the Ts65Dn mouse model [16].

SOD1 is the gene encoding for the enzyme that catalyzes the conversion of $O_2^{-\bullet}$ into H_2O_2 in the cytosol. The increase in SOD activity results in the formation of elevated levels of H_2O_2, and is not paralleled by similar elevation of CAT and GPX, thus leading to the overproduction of ROS. Accordingly, all DS tissues, in addition to the brain, display an altered SOD-1/GPX activity ratio [27] (Fig. 1). SOD-1 was found at levels approximately 50% higher than normal in a variety of DS cells and tissues, including erythrocytes, B and T lymphocytes, and fibroblasts. Another major contributor to the OS hypothesis of neurodegeneration in DS is the triplication of *APP* that is thought to have a key role in the pathology of AD. However, triplication of *APP* does not necessarily lead to enhanced expression of APP and subsequent Aβ accumulation, but it is strongly linked to Aβ deposition in adult life. As expected, in DS individuals, increased APP gene expression leads to increased production of Aβ [28,29], the major component of amyloid plaques that accumulate in brain in all DS individuals over 40 years of age. The levels of Aβ(1 − 42) and Aβ(1 − 40) are higher in DS plasma than controls and the ratio of Aβ42/Aβ40 is lower in DS than in controls [29]. In addition, the same group demonstrated that decreasing levels of plasma Aβ42, a decline in the Aβ42/Aβ40 ratio, or increasing levels of Aβ40 may be putative markers of conversion to AD in adults with DS, possibly reflecting compartmentalization of Aβ peptides in the brain. Several studies demonstrated that Aβ is associated with the production of ROS [30,31] (Fig. 1), and also induces calcium-dependent excitotoxicity, impairment of cellular respiration, and alteration of synaptic functions associated with learning and memory [32].

Moreover, it is worth to be mentioning that trisomy 21-induced ROS overproduction may itself alter APP processing, promoting intracellular accumulation of Aβ [12]. Thus, protecting DS brain from ROS may be of therapeutic value, although antioxidant supplementation has failed to show efficacy in preventing dementia in this population [33,34]. At the same time, overexpression of APP may promote mitochondrial dysfunction independently from aberrant Aβ deposition, thus exacerbating OS conditions [22].

Results from our group and others also suggest the involvement of *BACH1*, encoded on Chr21, in the regulation of the antioxidant response in DS. BACH1 is a transcription repressor that plays an important role in the regulation of the expression of genes involved in the cell stress response. BACH1, under physiologic conditions, forms heterodimers with small Maf proteins (i.e., MafK, MafF and MafG), which bind the antioxidant response elements (AREs) of DNA, thereby inhibiting the expression of specific proteins (Fig. 1). By contrast, increased OS levels suppress the function of BACH1 by promoting BACH1 nuclear export and enhancing the expression of its gene targets. When the intracellular heme levels increase, as under pro-oxidant condition,