Alzheimer's Disease & Treatment

Chapter 2

Down Syndrome for A Better Understanding Alzheimer Disease

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1. Introduction

A) Alzheimer disease (AD)

AD is the most common of dementia and affect millions individuals worldwhile characterized mainly by loss of memory and cognitive decline but also by sensory and motor impairments. Most AD cases are sporadic (SAD 98% of cases) at age more than 60 years but some have a genetic inheritance (2% around) at age earlier than 60 years and some at even 40 years [1]. The autosomal dominant AD (ADAD) are related to mutations on presenilin 1 (*PSEN1* ; chromosome 14 ; 18-50% ADAD cases) and presenilin 2 (*PSEN2* ; chromosome 1; *<5%* ADAD cases) and on Amyloid Precusor Protein (*APP* ; chromosome 21; 10-15% ADAD cases).

At the biochemical level, SAD or ADAD is characterized by extracellular deposits of synaptotoxic β-amyloid (Aβ) peptides, mainly Aβ40 and Aβ42 peptides in fibrils structures forming amyloid senile plaques (SPs) and by intraneuronal neurofibrillary tangles of anormally phosphorylated Tau proteins (NTFs) [2,3].

These neuronal changes induce progressive neuronal and synaptic deficits leading to many deficit including a progressive cognitive decline. They are present may years before the apparition of the early clinical symptoms and this window of more than 10 years may offer not only methods for early diagnosis but also early treatments in the disease process before it is too severe.

The SPs begin according to Braak stages mainly in the neocortex for phase 1, spreading to the allocortex and then in phase 3 to the diencephalice nuclei, the striatum and the cholinergic

nuclei of the forebrain, and in phase 4 and 5 to other brain nuclei and cerebellum [4]. SPs accumulation precede by many years the first clinical symptoms of AD but some individuals never develop dementia despite the presence of SPs. Aβ peptides are present under many species derived from the clivage by α and β secretases of the APP protein derived from the clivage by β and γ secretases of the APP protein but the main species are Aβ40 and A β42; these peptides undergo abnormal configurations which by spreading lead to aggregates present in SPs mainly due the hydrophobic 25-35 sequence of the Aβ [5].

NFTs are present in cell bodies and apical dendrites and in abnormal neurites. The neurofibrillary lesions are mainly due to aggregates of the tau protein which is abnormally phosphorylated in specific sites mainly on threonine 212 (7-8 mol of phosphate in NTFs instead of 2-3 mol in control tau protein [6]**.** Hyperphosphorylated Tau protein tends to dissociate from microtubules and thus induces axonal impairment. NTFs develop in the brain through six Braak stages starting as silent in the transenthorinal stage then to the the limbic stage for the incipient AD and at the neocortical stage for full AD [7]. Moreover tau hyperphosphorylation can be induced by Abeta soluble dimers [8].

Besides SPs and NTFs, neurotrophins such as BDNF (Brain-derived neurotrophic factor) and monoamines such as serotonin (5-HT: 5-hydroxytryptamine) are involved in AD since they regulate cooperatively some aspects of neurogenesis, neural plasticity and survival during aging in order to allow the brain to respond to environmental demands which may be very detrimenta. Many monamines ar modified in indivuals with Ad and in mice modelling AD [9]. In AD, BDNF is decreased in the hippocampus and the Aβ42 peptide might compromise BDNF both production and signaling, leading to neuronal degeneration [10]. Reduced 5-HT levels is one of the markers of accelerating cognitive decline in AD [11]. Other monoamines DA, NA are also reduced in certain brain areas (frontal and temporal cortex, hippocampus) from inviduals with AD but also in various brain areas from the APP/PS1 mouse model that develop cerebral amyloidosis [12]. Many patients with mild cognitive impairment (MCI) display some of the early clinical symptoms of AD. Among them some will be at risk for developping AD and some will not.

B) Down syndrome (DS)

DS is so far considered as the major genetic cause of intellectual disability. Down syndrome (DS) is a genetic disorder that results from the triplication of entire or part of chromosome 21 (Chr21) and occurs in 1 every 1000/1500 live births without family inheritance. Individuals with DS are not characterized by one symptom but present several pathological phenotypes which the accumulation of them induces the so-called DS phenotype which is highly variable among individuals and during aging [13]. Life expectancy in the DS population is shorter compared to non-DS individuals, but improvements in medical care and drug treatments have

significantly contributed to ameliorate the life quality of this population which now approaches 65-70 years and thus may be concerned with AD as the general population.

Although the increased dosage of Chr21 genes might be one of the causes of the phenotypical alterations of DS, the presence of trisomic genes also affects the expression of disomic genes, which, in turn, may gain aberrant expression and contribute to some clinical manifestations. Brain development defects induces intellectual disabilities which affect language, learning, memory but also motor, sensory and sleep deficits. Moreover it is reported that individuals with DS exhibit accelerating aging, behavioural abnormalities and early neurodegeneration which may be considered as major problems for this population.

Several early studies support the link between the DS phenotype and an increased risk of AD development [14 ; 15 ; 16]. The incidence of dementia among DS patients is 10% in the age range 35–50, 55% in the age range 50–60, and becomes 75% above the age of 60 years, but AD neuroanatomopathology is present in virtually all adults with DS older than 40 years. Despite these ubiquitous stigmates, the prevalence of dementia is variable ranging from 30-75% at age 65 and most of the cases of dementia in individuals with DS occur around 50-55 years. Nevertheless, there is a rather large subset of aged persons with DS who do not develop clinical signs of dementia at any age. Moreover it is reported that in peculiar cases, one woman of 78 years and one man of 65 years, the absence of the APP gene in triplicate leaves the individuals without the biochemical hallmarks of AD and consequently no dementia although they present the rest of the DS phenotype [17-18]. This rare patients confirm the crucial role of APP in the neuropathological and clinical findings of AD in individuals with DS. However, although plaques have been detected in young DS autopsy samples, and even in some fetal samples, it is only in late middle age that people with DS develop AD pathology [13;19]. The senile plaques are mainly due to the abnormal metabolism of the APP protein the gene of which is on chromosome 21 and the NTF are due to the abnormal phosphorylation of the Tau protein which might be partially due to some chromosome 21 phosphatases genes and also to some sAPPα dimers [8].

In the first study to comprehensively characterize DS samples with and without AD diagnosis in port-mortem brain samples and in the CSF, evident serotoninergic and noradrenergic deficits were found in DSAD versus early AD inviduals and to a lesser extent in DS versus healthy controls [20].

Although the clinical features and especially the time course might be different in AD in the general population and in individuals with DS, the biochemistry and pathology of AD in people with DS and in the typical population are essentially identical, the current « amyloid cascade hypothesis » is believed to apply to both populations. Thus, the population with DS represent the best human model to approach AD features several decades before the irreverible

dementia occurs.

2. Common Features between Individuals with DS and AD

The age of onset of dementia in individuals with DS is much earlier (35% at the age of 60 years) than the in SAD (70-80) but is similar (under 60) to the autosomal dominant AD (ADAD) [1].

Thus AD in DS individuals constitue the larger human group with a rather homogeneous genetic background to study the molecular pathways leading in some cases to dementia (DSAD) and thus allowing a window to test early markers and better understanding the course of this AD devasting disease.

Although**,** the definitive diagnosis for AD in the general population is often given post mortem by brain examination, many scales of evaluation of the cognitive deterioration are now used. Unlike familial AD, dementia in individuals with DS is still not well described although it accounts for the majority of genetic AD cases. The scales used for AD evaluations are not good enough fore a population like DS that has as at baseline some cognitive impairments especially in comprehension, memory and language. Nevertheless, the CAMDEX–DS has been validated as a reliable tool for assessing clinical dementia in people with DS [21], the Rapid Assessment of cognitive function in Down syndrome (RADD) [22] and the novel Behavioral and Psychological Symptoms of Dementia in Down Syndrome (BPSD-DS) are reported in [23], which in combination with an amyloid PET scan should increase the confidence of dementia of Alzheimer's type in DS. A good presentation of the similarities and differences between clinical presentations in DS, AD (or SAD) and ADAD also named FAD is given in the updated review par Zis and Strydom in which they report also the comparison of DS and AD for biomarkers [24].

2.1. Aβ peptides

Briefley, in the plasma Aβ40 and Aβ42 levels are higher in individuals with DS; in DSAD, Aβ42 tends to increase while Aβ40 decrease thus the ratio Aβ42/Aβ40 has not the same time course to evaluate dementia as in AD. In CSF, Aβ levels have been shown to increase in childhood and then decrease when SPs start to deposit similarly to what is observed in AD [19].

Positron Emission Tomography imaging (PETscan) with ligands such as [11C]-Pittsburgh compound–B (PIB) enables « *in vivo* » quantification and localization of fibrillar Aβ deposits and also tangles [25].

Higher PIB binding levels in cortical and subcortical regions of the DS brain were observed in participants with higher age, lower cognitive performance on neuropsychological assessment,

and in those with a diagnosis of dementia [26,27,28]. In their work by PET and volumetric RMN [29]: they conclude that results from populations with amyloid overproduction (DS and ADAD) compared to the general population may be generalizable because all populations accumulate the same amyloid aggregates and experience the same overall temporal progression of AD in which amyloid accumulation precedes neurodegeneration and dementia.

Increased global amyloid-β was related to decline in verbal episodic memory, visual episodic memory, executive functioning, and fine motor processing speed. Participants who were consistently PiB+ demonstrated worsening of episodic memory [30]. Other modalities are now developped such as diffusion tensor or retinal imaging to improve early diagnostic [31].

2.2. Tau

Microtubule-associated-protein tau is hyperphosphorylated and abnormally phophorylated in AD and aggregates in paired helical filaments (PHFs) in NTFs. The pretangle state, the intraneuonal tangles and the extyraneurocellular NTFs can be differentiated by specific to particular Tau epitopes [32].In general, NFTs follow a similar distribution in DS as in AD, starting in entorhinal cortex and spreading to hippocampus and later neocortex, but at a higher density in DS compared to AD brain. In the plasma the tau levels are higher in AD groups than in the general population. In individuals with DS these levels are also higher even in non demented ones [19].

2.3. APOE alleles and AD risk factor

APOE is a hepatocerebral lipoprotein that regulates the transport and deposition of cholesterol. Evidence suggests that harboring one or both apolipoprotein ε4 alleles (APOε4) may increase the risk for AD due to the apoE as an essential catalyst of the amyloid cascade and a subsequent loss of function [33,34].

Inheritance of one copy of the allele increases AD risk four-fold while inheritance of two copies increases risk ten-fold in the general population The APOε4 allele also increases dementia risk in DS, albeit to a lower extent than in AD. At the biochemical level this increased risk is porbably due to the presence of an amino-terminal apoE fragment in both the frontal cortex and hippocampus of the DS-AD brain [35].

2.4. Vascular pathology

Vascular pathology is common in the susceptibilty to AD in the general population. The contribution of vascular pathology to dementia may play a similar role in age of onset and/or the rate of progression of AD in DS (DSAD) [36]. Microbleeds (Bs) were more frequent in DS cases relative to controls but present to a similar extent as sporadic AD. This aligned

with cerebral amyloid angiopathy (CAA) scores, with more extensive CAA in DS relative to controls in both brain regions. CAA was also more frequent in DSAD cases relative to sporadic AD [37]. Moreover, as reported in the recent study that vascular or metabolic imaging might provide earlier information regarding AD pathogenesis [38]. In the hippocampus of older DSAD individuals, Myoinositol (MI) is higher, Nacetylaspartate (NAA) is lower and glutamate-glutamine complex (Glx) is unchanged when compared to non-demented people with DS.

2.5. Oxidative stress

Oxidative stress (OS) results from accumulation of oxidized and damaged molecules which are not removed by the antioxidant defense system (superoxide dismutases (SOD 1, 2 and 3), glutathione peroxidase (GPx), catalase etc) and thus can damage various cellular and extracellular components. The chronic SOD1 overexpression in all cells that characterizes the trisomy 21 subjects and the consequent over-generation of endogenous hydrogen peroxide apparently is not adequately compensated by the relatively modest upregulation of catalase and GPx. Therefore, this chronic imbalance between the levels of both important antioxidant enzymes (SOD/CAT+GPX) and their corresponding substrates inducing the generation of the most deleterious hydroxyl radical ($HO^{\cdot}$), might be the basis for DS disturbances. Biomarkers of oxidative stress are significantly elevated in DS [39]. The anti-oxidant system is affected in DS and this defect is worstened during aging [40]. The SOD1 has been shown to be elevated in the neocortex and the hippocampus of individuals with DS or AD [41]. Indeed loss of antioxidant enzymes and an increased in protein modification have been reported in AD [42, 43].

2.6. Mitochondria

Altered metabolism of APP might be related to mitochondrial dysfunction [44] and mutations in mitochondrial DNA have been related to AD changes in the general population as well as in the DS one [45].

Several studies have shown that alterations of mitochondrial structure and function associated with an impairment of reactive oxygen species (ROS) homeostasis are critically linked to DS pathogenesis. Deficits in energy metabolism due to mitochondrial dysfunctions negatively affect neuronal function, survival and central nervous system (CNS) development which requires ATP and occur as an early event in intellectual disability-linked diseases and several forms of dementia like AD [46]. Overexpression of APP may promote mitochondrial dysfunction in DS independent of aberrant Aβ deposition.

A recent review gives a survey of the role of michondria and its impaired functions in relation to oxidative stress both in DS and AD [47].

2.7. mTOR Pathway

mTOR influences Aβ deposition and tau aggregation and thus is associated with the pathogenesis and progression of AD and similarly in DS [28]. Briefly mTOR activation affects the regulation of Aβ generation/clearance and tau-phosphorylation by inhibition of the autophagy and by interaction with several key signaling pathways, including PI3K/Akt, GSK-3β, AMPK and insulin/IGF. Inhibiting mTOR activation for the treatment and prevention of AD and AD-like dementia in DS has been pointed but much work need to be done before going to a trial [28].

2.8. Endosomes

Intracellular Aβ is localized to endosomes which are responsible for the turn-over and the degradation of the proteins within cells. Early endosomes are a major site of amyloid precursor protein (APP) processing and a convergence point for molecules of pathologic relevance to AD. Neuronal endosome enlargement, reflecting altered endocytic function, is a disease-specific response that develops years before the earliest stage of AD and DS [48]. Endosomal pathology contributes significantly to Aβ overproduction and accumulation in sporadic AD and in AD associated with DS and may signify earlier disease-relevant disturbances of the signaling functions of endosomes. One of the main point regarding endosomes is that large endosomes might be an hallmark for early detection for AD in DS and also for AD in the general population. More recently enlarged endosomes were detected in blood mononuclear cells and lymphoblastoid cell lines (LCLs) from individuals with AD using immunofluorescence and confocal microscopy showing that it may be a biomarker [49]. The volumes of enlarged endosomes correlate to [C11] PiB cortical index but not to the amyloid-beta, tau and phosphorylated tau levels measured in the cerebrospinal fluid. Moreover the enlargment of endosomes in DS is at least partially due to synaptojanin present in three copies [50].

2.9. Mis-segregation in AD

In their analysis [51] of thousands of cells from 27 AD and 13 control individuals showed that fibroblasts from AD patients were more than twice as likely to exhibit trisomy 21 compared to fibroblasts from control individuals. The increased frequency of trisomy 21 cells in fibroblasts from AD patients was significant and independent of age. Furthermore, the chromosome mis-segregation was associated with all types of AD, including sporadic and familial AD carrying a mutation in either PS1 or PS2.

3. Differences Between DS and AD Regarding Pathological Aging

3.1. Clinical aspects

In the DS population, the prevalence of dementia increases rapidly after the age of 30

years although data are very different from the very few cohorts studied. The overall prevalence of dementia in adults with DS is estimated at 6.8 % with an increase with age from 8.9 % in individuals up to 49 years to 32.1 % in individuals from 55 to 59 years old but it has also been reported higher as 33% among individuals with DS aged 30 to 39 years, 55% among those aged 40 to 59 years, and 77% for individuals above the age of 60 years. It should be point out that individuals who nowadays reach old ages are those who did not have cardiac abnormalities which most often were letal without cardiac surgery available since 30 years in developped countries [19 ; 29]. A recent study shows some predictions about survival of people with DS according to the occurrence of AD [52].

By comparison, the prevalence of dementia in the general population is estimated as 4% below 65 years, 15% between 65 and 74 years, 43% between 75 and 84 years, and 38% over the age of 85 years [29].

3.2. Amyloid and tau aspects

The early study on 42 cases of DS under 40 years demonstrate the Aβ deposition within the hippocampus and parahippocampal gyrus prior to NFT in neurons or dystrophic neurites within SPs [53]. Moreover in this study and others it is reported that Aβ deposition in childhood and teens might be more frequent than previously estimated in DS and also than in the general population. Both infants, children and teens with DS accumulate intracellular Aβ prior to the accumulation of extracellular Aβ deposits [54].

Aβ production from APP nonspecific proteolytic cleavage leads to heterogeneous Aβ (including Aβ40/42/43) in a possible endosomal/lysosomal location [55]. There is an accumulation of intracellular Aβ within neurons in DS at a much earlier age than in the general population. Moreover Aβ measured biochemically increase during aging suggesting an acceleration phase to disease development [56].

Schupf and colleagues reported that increasing levels of plasma Aβ40 and decreased Aβ42 were in DS good predictors of conversion to dementia [57]. Indeed, adults with DS with decreasing plasma 42 over time were 5 times more likely to become demented within 4 years. Similarly, in a separate prospective study on 405 persons with DS, those adults in the highest levels of plasma Aβ42 and Aβ40 also had the highest risk of developing dementia over an average 4.7 year period of time [58].

PIB binding in DS, first appearing in striatum, began around age 40 and was strongly associated with dementia and cognitive decline. The absence of a substantial time lag between amyloid accumulation and cognitive decline contrasts in sporadic/familial AD [27]. The study by PET imaging [59] has shown that in DS brain, Aβ binds to (18F) florbetaben and that this binding increases with age. Increased global amyloid-β was related to decline in verbal

episodic memory, visual episodic memory, executive functioning, and fine motor processing speed. Participants who were consistently PiB+ demonstrated worsening of episodic memory [60].

Regarding β amyloid peptides, it is interesting to note that BACE-2, a chromosome 21 protein which activates BACE1, was observed only in neurons of adults with DS but not in young people and in individuals with AD.

Few studies have focused on tau proteins in the course of AD in DS but a recent one shed a new light on this old controverse about the first hallmarks in AD [61].

3.3. Other biochemical aspects

As in the AD brain, the majority of proteins have been demonstrated to be oxidized (OS), thus the notion that aberrant protein oxidation in DS may contribute to AD development is relevant. In DS brain, despite increased OS levels, no changes in HO-1 protein levels has been observed in young subjects, whereas increased levels characterize adult DS subjects undergoing AD-like neurodegeneration. Interestingly, increased of HO-1 in DS/AD subjects is not comparable with that observed in AD subjects. This phenomenon seems likely linked to the trisomy of chromosome 21 BACH1 gene, which encodes for the nuclear repressor of HO-1 gene [62]. Indeed HNE modified proteins have been shown in excess in DS brain [63].

Accumulating evidence also suggests that impaired iron homeostasis is an early event in AD progression but also in DSAD [64]. Iron dyshomeostasis leads to a loss of function in several enzymes requiring iron as a cofactor, the formation of toxic oxidative species, and the elevated production of beta-amyloid proteins. DS might represent a specific case of genetically encoded OS. Indeed, there are a number of trisomic genes, that directly or indirectly affects ROS levels, either by causing increased ROS production or decreasing the antioxidant response [65]. The molecular mechanisms linking iron dysregulation to neurodegeneration in DS are still poorly understood.

4. Chromosome 21 Genes Involved Directly or Indirectly in AD

The entire sequence of human Chromosome 21 is now known and there are 233 coding genes, 299 long non-coding genes (Ensembl release 78) and 29 microRNAs (miRBase release 21). 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 81different 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 [66].

Some chromosome 21 genes might be important to better understand directly AD. Moreover some of chromosome 21 genes can regulate other genes and signalling protein involved in AD. The most important chromosome 21 genes known now to be involved in AD are : APP, BACE2, BACH1, DYR1A, ETS2, RCAN1, S100β, SOD1, SYNAPTOJANIN. These genes encode proteins which have been shown to be important for some of the DS phenotype including the AD [67].

- **APP**

The gene coding for the APP protein is on chromosome 21 and its promoter is regulated by Ets-2 an another gene of chromosome 21 which is overexpressed in DS explaining at least partially the fact that APP is more than 1.5 expressed in DS cells and tissues. APP has already be mentionned previously as the source of the amyloid peptides which due to their abnormal folding will lead to agregates and later on to fibrills [68]. But it should be also point out that the proteolytic cleavage by α secretase gives the sAPP α extracellular fragment which has been shown to be beneficial for some cognitive functions especially memory, for neurite outgrowth, prevents A β generation and tau phosphorylation, counteract the A β effects and finally disrupt APP dimers [69]. The sAPP α extracellular fragment is present at lower levels in individuals with AD than in controls. Its potential beneficial role from an ombilical cord source has been recently assayed in animal models for AD and shown to be mediated by complement C1q [70].

- **BACE-2**

BACE-2 cleaves APP, is increased in DS and thus contributes to increased Aβ production [71. Moreover BACE-2 activates BACE1, one of the proteolytic enzyme of the amyloid cascade [72].

- **BACH1**

BACH1 is a basic leucine-zipper protein and the nuclear repressor of HO-1 gene. Increased Bach1 expression levels are involved, overall, in repressing the induction of HO-1 in DS cases, thus reducing HO-1 overexpression in stress conditions as observed in AD. Overexpression of BACH1 is also related to oxidized species [62].

- **CBS**

CBS levels in DS brains are approximately three times greater than those in the normal individuals and CBS is localized to astrocytes and those surrounding senile plaques in the brains of DS patients with AD [73]. CBS is the main enzyme producing H_2S. CBS activity is reduced in AD brains and the decrease in H_2S may be involved in some aspects of the cognitive decline in AD [74]. Moreover, several experiments have shown in different rat or murine

models of AD that H_2S could be beneficial [75].

The CBS overexpression induces monoamine pathways alterations in various brain areas of CBS transgenic mice according to sex and age [76]. Thus these alterations by CBS over-expression might be involved in the developmental abnormalities in cognition in DS children and that may lead to AD in DS adults.

- **DYRK1A**

The DYRK1A gene encodes the protein DYRK1A which is a serine/threonine kinase. Dyrk1A is overexpressed in SPs from AD individuals and is a key molecule bridging β-amyloid production and tau phosphorylation in AD [77]. It phosphorylates tau protein making it a better substrate for GSK3β phosphorylation, and DYRK1A phosphorylates alternate splicing factors leading to an increase ratio of 3R:4R tau, which is associated with neurodegeneration ; consistent with this finding, there is an increase in the number of DYRK1A-positive and 3R-positive NFTs in middle-aged and older DS brain compared to sporadic AD [78]. Overexpression of DYRK1A it at least partially responsible for the excessive synaptic inhibition in people with DS which can be reverses both in individuals with DS and in animal models by inhibiting DYRK1A with catechol compounds [79; 80; 81]. Moreover DYRK1A overexpression modulates monoamines neurotransmitters in transgenic mice altering both the serotoninergic and the dopaminergic pathways [82].

- **ETS2**

Overexpression of ETS2 in DS may play a role in the pathogenesis of the brain abnormalities in DS and possibly AD [83]. Degeneration of DS neurons was reduced by dominant-negative ETS2, suggesting that increased ETS2 expression promotes DS neuronal apoptosis. In the human brain, ETS2 expression was found in neurons and astrocytes. Strong ETS2 immunoreactivity was observed in DS/AD and sporadic AD brains associated with degenerative markers such as Bax, intracellular Abeta, and hyperphosphorylated tau [84].

- **RCAN1**

RCAN1 levels are increased in the brain of DS and AD patients but also in the human brain with normal aging [85]. RCAN1 has been implicated in several neuronal functions including hippocampal plasticity. Its overexpression is involved in AD [86]. It is also involved to control the tightly coordinated process of fission/fusion in mitochondria (parra) and thus it induces mitochondrial defects seen in aging and AD [87]. Moreover RCAN1 increases susceptibility to oxidative stress.

- **S100β**

S100β expression levels are increased in both DS and AD astrocytes in association with neuritic plaques [88]. In addition, chronic overexpression of S100β contributes to increased neuronal and neuritic APP expression with consequent accelerated amyloid deposition, as well as abnormal growth of neurites in β-amyloid plaques, similar to observations in middle-aged DS patients [89].

- **SOD1**

The SOD1 is localized in the neocortex and hippocampus from individuals with DS or AD [41]. The SOD1 activity is increased and not compensated by catalase or GPX thus leading to the overproduction of ROS.

SOD1 overexpression induces aberrant neuronal and mitochondrial proteins in hippocampus of transgenic mice [90] and alters the 20S proteasome during aging [91, 92]. The anti-oxidant system is affected in DS and this defect is worstened during aging [40]. It is also altered in AD [42].

- **Synaptojanin**

The phosphoinositide phosphatase synaptojanin 1 (SYNJ1) is key regulator of synaptic function Synaptojanin (Synj) and a dual phosphatase which regulates the Hedgehog pathway (Hh). It has been shown that reduction of Synaptojanin 1 (SYNJ1), the main phosphoinositol (4,5)-biphosphate phosphatase (PI(4,5) P2-degrading enzyme) in the brain and synapses, accelerates Aβ clearance in AD mice model [93]. It is overexpressed in DS brain and in APOE4 carriers with early AD and highly overexpressed in individuals with DS/AD [94].

Synaptojanin is involved in the homosostasis of inositols compounds and is overexpressed in DS brain [95]. Its metabolism is altered in the brain of Ts65Dn mice, the most commonly used model of DS. This defect is rescued by restoring SYNJ1 to disomy in Ts65Dn mice and is recapitulated in transgenic mice overexpressing SYNJ1 from BAC constructs [96]. It has been shown to be involved in the aging hippocampus memory deficits in thre models of AD [97].

5. Animal Models to Study AD in DS Models

The first models for Down syndrome were transgenic mice for some key genes such as SOD1, APP, S100β and CBS and some knout-mice for some of them were also useful to understand the role of some of these genes either solely or in a complex genotype. Human chromosome 21 has orthologous genes on MMU 16, 17 and 10 and most of the partial trisomic murine models have been reviewed in [81; 98].

The first partial trisomic viable model, Ts65Dn, has been developed by Muriel Davisson

in the early 90's [99] and is trisomic for about 120 orthologs of Hsa21 protein encoding genes through a segmental trisomy for Mmu16 but it contains also a segment of about 10 Mb of the Mmu17, which contains 60 protein encoding genes, none of which are homologous to Hsa21 genes

Another mouse model for DS, Ts1Cje, has shorter Mmu16 trisomy than the Ts65Dn mouse, contains 62 orthologs of Hsa21 genes, and excludes the gene segment containing APP and SOD1.

The Ms1Ts65 mice are trisomic for the region of difference between Ts1Cje and Ts65Dn, contains 56 orthologs of Hsa21 genes within genetic segment from Mrp139 to Sod1. Another relatively novel model for DS is the Ts2Cje mouse model Ts (Rb (12.1716)) 2Cje (Ts2).

A more accurate mouse model for DS model have been developed by the team of Yu that carries complete aneuploidy (spanning the entire Hsa21 syntenic region) the triple aneuploid mice contains the Mmu10 (Ts1Yey), the Mmu 17 (Ts2Yey) and the Mmu16 (Ts3Yey).

A notable DS model was created from the trans-species insertion of Hsa21. The Tc1 mouse model for DS carries most of human chromosome 21 in addition to the normal complement of mouse chromosomes, and is trisomic for approximately 212 Hsa21 protein-encoding genes but not the APP gene [100].

The relationships betwwen these models and their properties in relation to alzheimer disease are presented in [101,102].

DS mouse models have also been investigated for better understanding the role of different gene segments of Hsa21 on AD pathology and memory impairment associated with DSAD. In these models some of the DS characteristics have been investigated regarding cognitive deficits biological mechanisms involved in DSAD including extracellular amyloid β protein (Aβ) accumulation, intraneuronal neurofibrillary tangles (NFTs) deposition, BFCN cell loss, neuron loss in locus coeruleus (LC), hippocampal abnormalities, imbalance of neurotrophic factors, alterations in long-term potentiation (LTP), abnormal endosomal signaling, presence of neuroinflammation and oxidative stress and more recently neurotransmitters.

The results obtained in these different models have been reported in recent studies [101;103] and most of them have been used to pre-clinical approaches. More recently a new model for studying AD and especially preclinical stages have been developped using a rat injected by adeno-associated viruses (AAV) coding for human mutant APP751 containing the Swedish and London mutations and PS1 (the M146L mutation) cDNAs into the hippocampi adult rats [104].

Before describing the pre-clinical approaches, we will developped a small paragraph

on neurotransmitters as we think that the abnormalities in neurotransmitters contents have not been enough considered in preclinical approaches.

5.1. Neurotransmitters

The monamine system has been studied in a few studies either from post-mortem brain tissues from individuals with AD or DS or both DSAD and in some animal models. Briefly in human tissues, a reduction of noradrenergic and serotonergic pathways were measured pathways in DSAD versus early onset of AD (EOAD) and to a lesser extent in DS versus controls [20]. DS and DSAD present similar monaminergic profiles which might be related to early amyloid deposition in DS.

A recent study was performed on APP/PS1 mice [12] and showed no age effect in control mice according to age 6, 12, 16, 24 months but a region sepcific changes for all monoamines in 18 months APP/PS1 mice compared to controls.

The monoamines pathways evaluated in young Ts65Dn mice versus controls showed that a) the noradrenergic system was mainly affected by aging and not aneuploidy, b) the dopaminergic system was barely affected in Ts65Dn, c) the serotonergic was reduced (5-HT and 5-HIAA levels) in the hippocampus of young Ts65Dn versus controls but not in aged ones [105]. These results are quite different from those obtained transgenic mice overexpressing the single DYRK1A showing major deficits in serotonin contents for the four brain areas and major deficits in dopamine and adrenaline contents especially in the hypothalamus [82]. These differences between the two studies might be due to compensation between different chromosome 21 genes and non chromosome 21genes present in the Ts65Dn mice.

The same type of studies should be performed on transgenic mice for important T21 genes related to DS and neurotransmission as it was done for CBS trangenic mice [76] and also in other models of T21 especially in rat models which seem to be more accurate to study AD in DS [106].

Neurotransmitters-bases strategies are plausible for targeting cognitive decline in AD and DS [107,108].

6. Pre-Clinical Approaches for AD in DS Models

A) *Search for biomarkers*

In the same time as researchers are trying to find therapeutical approaches, much work is done to find biomarkers for the conversion of AD in individuals with DS. These biomarkers found either in DS or in AD non DS will benefit for both of the populations.

In DS, the higher levels of Aβ40 or Aβ42/Aβ40 correlates with the onset of AD in

DS. The formation of tangles is correlated with cognitive decline and PET studies of glucose metabolism might provide evidence of brain atrophy and AD changes in DS. Moreover as reported in the review by [109], many other markers show either decreases or increases; proNGF, MMP'1, TNFα, IL6, IL-10, SAH, SAM/SAH (from the chromosome 21 CBS gene) exhibit higher levels while serum MHPG, CSF orexin A show lower levels.

The combined use of DYRK1, BDNF (brain-derived neurotrophic factor) and homocysteine measured in the blood of two unrelated AD patient cohorts and age-matched controls has showed to give a sensitivity of 0.952, a specificity of 0.889 and an accuracy of 0.933 in testing for AD [110]. The same approach is currently used for DS in the progression of DSAD.

The rat model using AAV (AAV-AD) identified in the plasma of the various aged animals 41 proteins at 8 months and 21 proteins at 30 months which are specifically dysregulated in the course of AD pathology and thus identifying several steps before acute clinical hallmarks [104].

B) ***Inhibition of some DSAD hallmarks***

Oxidative stress is a link betwwen AD and DS [111]. Although since many years, treatments have been focused on antioxidants without real therapeutical progress, a study shed new light at the antioxidant status in the blood of DS children, before and after 6 months of daily antioxidant supplementation with vitamins E and C [112]**.** Before the antioxidant therapy, DS patients presented decreased GST activity and GSH depletion; elevated SOD, CAT, GR, GGT and MPO activities; increased uric acid levels; while GPx and G6PD activities as well as vitamin E and TBARS levels were unaltered. After the antioxidant supplementation, SOD, CAT, GPx, GR, GGT and MPO activities were downregulated, while TBARS contents were strongly decreased in DS. The same type of study should be done as the result obtained in a survey of trials with vitamin E only in mild cognitive impairment and Alzheimer's individuals fail to improve cognitive function, global severity or activities of daily living [113]. Other anti-oxidant compounds should be more investigated : Coenzyme Q10, curcumin to induce BDNF, melatonin.

- Inflammatory processes in BFCN degeneration can be modulated by minocycline treatment which inhibits microglial activation, prevents progressive BFCN decline and markedly improves performance of theTs65Dn mice on a working and reference memory task [114].

- mTOR signalling and its aberrant modulation in DS and AD age-related cognitive decline affects crucial neuronal pathways. It was recently reported that intranasal rapamycine reverse many AD hallmarks. Indeed in the Ts65Dn mice this treatment could reduce APP

levels, APP processing and APP metabolites production, as well as, tau hyperphosphorylation and a reduction of oxidative stress markers [115].

- Modulation of neurotransmission. The group of Saheli has focused since many years on the possiblity that neurotransmitter-based strategies and more sepcifically the noradrenergic system could be a target therapy for DS and AD [107; 108]. The GABAergic system is also a good approach and the use of antagonists of GABA receptors including pentylenetetrazol (PTZ) to reduce perturbations of the excitatory/inhibitory balance towards an excess of GABA might be fructful despite negative results up to date [81; 116]. Neurodegeneration can also be at least prevented by estrogen treatment which partially rescued working memory (T-maze test) and prevented neurodegeneration in aged Ts65Dn animals (11 to 17-months old) [117, 118].

- Regarding the endosome abnormalities, partially reduction of β-secretase1 (BACE1) by deleting one *BACE1* allele blocked development of age-related endosome enlargement in the medial septal nucleus, cerebral cortex and hippocampus, and prevented loss of choline acetyltransferase (ChAT)-positive medial septal nucleus neurons. It was also reported the possibility that studies focused on dysregulation of signaling endosome may identify some therapeutic targets for preventing DSAD [10].

- Exosome has been shown as a therapeutic approach for neurodegenerative disease [120]. Exosome secretion is enhanced in the brains of DS patients, in a mouse model of the disease and in DS fibroblasts. Furthermore, increased levels of the tetraspanin CD63, a regulator of exosome biogenesis, were observed in DS brains. As CD63 knockdown diminished exosome release and worsened endosomal pathology in DS fibroblasts, it was shown in the Ts65Dn mice that the increased CD63 expression enhanced exosome release to mitigate endosomal abnormalities in DS [121]. Exosome might be a biomarker for AD in DS [122].

- APP metabolism modulation

It was shown that long-term exposure to environmental enrichment reduces Aβ oligomers and rescues spatial-memory abilities in 12-month-old trisomic mice [123].

The Ts65Dn mice, as a model for DS and also for DSAD has been used for immunisation against Abeta oligomers [124]. In the States AC Immune and UCSD represents the first major clinical trial by a pharmaceutical company for Alzheimer's in the Down syndrome population. The study is focused on developing a vaccine that targets the amino acids of the Aβ peptides specifically involved in their misfolding, thus preventing their aggregation, the formation and plaque accumulation, and promoting plaque removal.

- Inhibition of DYRK1A

EGCG (Epigallocatechin-3-gallate) inhibits DYRK1A activity in vitro in several murine models of DS and mice treatment with EGCG restores some of the DS-associated deficits present in these models [79]. EGCG is not only an inhibitor of the biological activity of DYRK1A but it also binds the Tau protein in its phosphorylated region, hindering the access of this region to some kinase and modyfying the tridimentional structure of the protein. These three combined functions of EGCG regarding Tau protein prevent its aggregation which is a key protagonist of neuronal cell death [125]. EGCG shows protective effects against Aβ-induced neurotoxicity and regulates secretory processing of sAPPα via the PKC pathway. Administration of EGCG (2 mg/kg) to mice for 7 or 14 days significantly decreased membrane-bound holoprotein APP levels, with a concomitant increase in sAPPα levels in the hippocampus. The role of EGCG in relation to AD is reveiwed by [126]. Combined treatment with environment enrichment and EGCG ameliorates learning deficits and hippocampal alterations in Ts65Dn mice [127]. New DYRK1A inhibitors are currently studies in amny laboratories [128, 129].

C) *Induced pluripotent stem cell (IPs) and deciphering AD in DS*

The use or pluripotent stem cell technology has given dramatic increase in our possibility for a better knowledge of the mecanism and the development of drugs in neurodegenerative disease [130]. A new inhibitor of DYRK1A, nammed ALGERNON (altered generation of neurons) was found in a screen for of neural stem cells (NSCs) [131]. This compound was found to rescue proliferative deficits in Ts65Dn-derived neurospheres and human NSCs derived from individuals with DS. Moreover, administration of ALGERNON to pregnant Ts1CJe dams rescued aberrant cortical formation in DS mouse embryos and prevented the development of abnormal behaviors in DS offspring. These data suggest that the neurogenic phenotype of DS can be prevented by ALGERNON prenatal therapy. As part of the neurogenic phenotype is also connected to AD, this type of experiments can lead to further evaluate if these corrected mice will present also some rescue of the DSAD phenotype although the Ts1Cje mice do not have the APP gene in triplicate.

Another recent study show promissing results regarding AD, by the use of pluripotent IPSc from DS individuals [132]. It could be shown that in vitro generated DS neural cells have abnormal Aβ metabolism and increased expression of AD-associated chromosome 21 genes (BACE2, RCAN1, ETS2). These results show that it is possible to study AD-type pathology through the study of IPSC from DS individuals.

7. Conclusions

The close relationships between chromosome 21 genes involved in the onset of AD in the general population and their presence in third copies in individuals with DS yield new opportunities to better understand the course of AD, find biomarkers and innovative therapies for AD in the general population (SAD) through the precise study of the course of AD in

this special genetic population (DSAD). It is crucial to identify biomarkers for AD in this population so as to be able to determine the efficacy of any new treatment early in the course of the underlying disease process and well before the AD-related pathology and cerebral atrophy have become established.Thus the numerous mice models present for DS and their combination with others such as those silencing specific chromosome 21 gene are and will be very useful to assay new drug therapies. But mice are not men and the main important persons are those with DS or AD or both. In that perspective, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute on Aging (NIA), both parts of the National Institutes of Health, are partnering on an initiative to identify biomarkers and track the progression of Alzheimer's Disease in adults with DS. Moreover AC Immune and UCSD are trying to develop for individuals with DS a vaccine specific for the abnormal folding of the abeta peptides.

8. References

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