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Review Paper

A SIX-STEPS TRIP INTO MOLECULAR-GENETIC IMPLICATIONS OF ALZHEIMER-PERUSINI'S DISEASE

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Abstract

Alzheimer-Perusini's disease is the most common dementia underlying pathology around the world. Although it relies on a series of well-known pathognomonic hallmarks (i.e., β-amyloid plaques and neurofibrillary tangles), many doubts remain about its etiopathogenesis. As happened with other little-known diseases, genetics might shed lights on its mechanisms of occurrence. The aim of this review is discussing about genetic studies in this field, without neglecting an assessment of their relative relevance. Hence starting from a comparison between GWAS analysis and little family study, we will describe the pathogenic role of six gene in Alzheimer-Perusini's disease pathogenesis. Three of these (*SORL1*, *ABCA7* and *BIN1*) are involved in endolysosomal trafficking and processing of amyloid precursor protein (APP). Another one, ABI3 is relevant for cellular chemiotactic movement, for example the directed displacement of microglia aimed at β-amyloid fibrils phagocytosis. In addition, we covered CLU/APOJ (a particular apolipoprotein) functioning, that seems to be essential for plaques clearence. Finally, we described also ADAMTS1 a metalloproteinasis, which acts on Aβ in extracellular environment. In particular, we have mentioned some genetic peculiarities of the atypical forms, which probably represent the most interesting Alzheimer-Perusini's pathology subset, because of its high (more than mendelian ones), but not very high (less than sporadic forms) number of associated gene, which also corresponds to an intermediate environmental influence.

Key Words: Genetics; Alzheimer-Perusini's disease; Neurodegeneration; Endolysosomal pathways; Microglia.

1 Introduction

"Neurodegenerative disease" is a locution which designs a large range of illnesses, that are characterized by neuronal death, and therefore synapses loss (resulting in connectome deficits). These are tipically progressive and their symptomatological spectrum evolution is strictly

bound to the specific neuronal damaging trajectories. Other main feature is the coexistance of multiple protheinopaties, which are ultimately responsible for cellular death. Classically, the most represented protein accumulation constitutes a differential criterion between various pathologic entities which implies nervous tissue destrunction, although a lot of overlappings remain unsolved. Alzheimer-Perusini's disease is the most widespread neurodegenerative disease around the world, and a recognized public health problem [1], causing the most common dementia form. As studied by Alois Alzheimer and Gaetano Perusini about ten decades ago, neuropathologic hallmarks are: β-amyloid plaques and Neurofibrillary tangles; hence the main AD taupathies. Neurons seems to die for necroptosis [2]. The former contains mainly clivage product of amyloid precusor protein (APP), $A\beta_{39-43}$ fragments, and a wide spectrum of diverse macromolecules, especially other proteins (i.e., synaptic proteins) and lipids. The latter are made up of hyperphosphorilated tau protein paired helical filaments. Tau is a microtubule stabilazing protein, thus when it is dysfunctional, we are witnessing the microtubule catastrophe, which will result in axonal transport deficit. In amnestic AD form, Ippocampal CA1 neurons are the first nuclei to be affected. Not by a chance, in major part of cases, the onset symptom is a dysfunction in establishment of long-term memories, whose "house" in the brain is right in the hippocampus. Amnestic (typical) AD is a sporadic and late onset form (after 65 years old). However, G. Perusini had already described early onset (before 65 years of age) AD dementia cases, for which a strong basic genetic nature was later recognized. In particular two main categories could be distinguished: Mendelian and Atypical. The are three causative genes: APP, PSEN1 and PSEN2, which are responsibile for certain AD familiar subtype (mendelian inheritance); two storically associated genes: MAPT (tau genic locus) and ApoE (ε4 allele recognized as major risk factor after age); and a myriad of estimated associated genes. This last constitutes the genomic scenario underlying atypical forms. This incredibly complex genetic background along with the totality of the energy variations of the external environment (so-called stimuli), which are reflected instant by instant in variations of the internal environment, could explain the notable differences between one atypical form and another. Nevertheless, every single atypical AD patient probably represents a unicum by a molecular genetic point of view. However, today, atypical AD forms are usually discriminated into 5 subdivisions: 1) Posterior cortical atrophy (PCA); 2) Logopenic variant of primary progressive aphasia (LvPPA); 3) Behavioral variant of AD (BvAD); 4) Dysexecutive variant (dAD); and 5) AD with corticobasal degeneration. 3) and 4) originates from the previous definition of Frontal AD, which today is largely retained imprecise and misleading, as the involvement of the frontal lobe is not so marked or even less exclusive [3]. At this point, it is natural for our synapses to prompt us to ponder the true significance of conducting a comprehensive genetic investigation in this context and the potential value it holds in terms of outcomes. At first glance the answer can only be threefold: a) it could help us to understand the molecular underlying mechanism *in toto*; b) hence it could give the possibility to identify new early biomarkers; c) likewise, it could give basic elements in order to project a genic, cellular or RNA interference-based therapy (or in general other therapeutic landscapes).

2. Genome-wide association (GWAS) and "small" familiar studies

In the previous introductive paragraph, we spent some words about the significance of genetics in multifactorial diseases. Investigations in this sense are aimed at reconstructing a *genetic architecture* of the disease, which was defined as the variants panel with an influence on the pathological phenotype, along with their effects intensity, population frequency and the way in wich they interact between them and the environment in general [4]. The heritability of AD dementia is estimated to be between 60 and 80% for Gatz et al (Gatz et al. 2006), instead in other

two works (Lambert et al. 2013; Liu et al. 2017) was reported that hereditability ranging from 90-100% in EOAD and 60-80% in LOAD. As reported in an article written by Khani et al. in 2022 [5], searching for AD rare variants is usually considered arduos and challenging, but, at the same time, very promising; surely NGS platforms (in particular third generation ones) come in our aid. In order to rebuild AD genetic architetture, we can distinguish two main ways, that really open a huge spectrum of potential methods. The former is GWAS studies, which permit to establish the distribution of a given variant in AD patients and controls worldwide; the latter are represented by the genetic analysis of family with a well characterized disease history. Given that scientific community present and future main objective is the achievment of personalized medicine, we cannot disregard either of the two approaches: starting from a single family, we still must refer to GWAS studies to estimate the distribution of the variant in affected people around the world. On the other hand, each individual case of AD, particularly as regards the atypical forms, seems to constitute an entity in itself, therefore the statistical values resulting from a GWAS risk having a much-reduced significance at the assessment level of the single affected patient. Surely these approaches will have to be followed by involved pathways analysis and above all functional assay and *ad hoc* experimental animal models, in order to hypothesize the effects of selected variants and verify them *in vitro* and *in vivo*.

The first GWAS in AD [6] identified just APOE as a risk locus, probably because of the small sample size. This meant not just reinventing the wheel, but also confirming the APOE central role as major risk factor, compared to the set of minor contributions provided by all other variants. A big step forward in this sense was made later when the European Alzheimer and Dementia Biobank (EADB) consortium brings together the various European GWAS consortia already working on Alzheimer-Perusini's disease. Hence, a novel dataset of 20464 clinically diagnosed AD cases and 22244 health controls has been collated from 15 European countries. A more recent GWAS study was conducted by C. Bellenguez et al. [7], in which they realized a two-stage genome-wide association study totaling 111326 clinically diagnosed or "proxy" AD affected individuals and 677663 healthy controls. They found 75 risk loci. 42 loci of those were new at the time of analysis. In addition, this reaserch group built a novel genetic risk score bound to future AD/ dementia or progression starting from mild cognitive impairment (MCI) to AD/dementia. For what concern GWAS for atypical AD, the relative rarity of these forms makes it challenging to conduct large-scale genetic studies with adequate statistic power [8]. Anyway, a GWAS in PCA identified candidate genes implicated in developmental and intercellular communication processes in central nervous systems (CNS); findings requiring replication and validation [9]. In this last analysis, J. M. Schott and colleagues genotyped 302 PCA patients from 11 centers, computed risk at 24 loci for AD/DLB and realized an exploratory GWAS. They found 3 new associated loci: rs76854344 near CTNAP5; rs72907046 near FAM46A; and rs 2525776 near SEMA3C. Regarding familiar studies, for istance, we can report one work[10], where authors performed an exome sequencing analysis on a Jewish Istraeli consanguineous family, which come from Morocco and was clinically diagnosed with EOAD. They identified a homozygous mutation (p.Gly415Arg) in CTSF (Cathepsin F; 11q13.2 gene [11]) as the most likely causative variant [10].

In the following sections we will talk about some genes found in these studies, focusing on its potential pathogenic role.

3. Six involved genes or six steps toward complete pathogenic mechanism knownledge?

3.1 *SORL1*

SORL1 encodes for the protein Sortilina A (SORLA) and was, at beginning, retained as an LDL receptors family member [12]. Subsequently, SORLA was classified as one of five mammalian sorting receptors which present a vacuolar protein sorting domain (VPS10) [12-15]. Early

studies showed a loss of SORLA expression in sporadic Alzheimer-Perusini's disease (SAD) brain neurons [16, 17]. SORLA acts as a receptor with function of adaptor protein for the retromer complex [18, 19]. This retromer complex constitutes a key element of the endosomal protein sorting system. It works by recognising specific membrane proteins – cargo – that are concentrated into discrete regions of the endosomal membrane, in which tubules begin to grow, tubulin monomer by tubulin monomer, and thus transport the cargo to the appropriate destination. Cation independent mannose 6-phosphate receptor (CIMPR) [20, 21], Iron transporter DMT1-II/Slc11a2 [22], Wnt transport protein Wntless/MIG-14 [23], Crumbs (Crb) [24], an apical protein required for cell polarity, and SorL1 (sortilin-related receptor, also known as SorLA) represent relevant examples of retromer cargoes. SorlA is necessary for various receptors sorting in endolysosomial system; for istance important neurotrophic factors such as BDNF (https://www.alzint.org/resource/world-alzheimer-report-2021, GDNF [25] or insulin [26] receptor. SORL1 retains APP in the trans-Golgi network, preventing it from transiting through the late endosomes, where Aβ40 and Aβ42 [27] appear to be produced. It is also able to target newly produced Aβ peptides to lysosomes, where they will be degraded, but does not affect the transport of APP from the endoplasmic reticulum (ER) to the Golgi [28]. In mice knock out for SORLA phosphorylated synapsins accumulates in various regions of the brain. This suggests a possible role for SORLA in the degradation of synapsins, which, in turn, could affect synaptic vesicle endocytosis [29]. Moreover, Huang et al. exploited SORLA transgenic mice to show an interaction with the ephrin receptor EphA4, that is relevant for the maintenance of synaptic structure and function [30]. Aberrant EphA4 activation by Aβ has been described in AD by two works, [31, 32]. Nevertheless, SORLA interaction with EphA4 was demonstrated to prevent synaptotoxic activation of this receptor [30]. SORL1 loss conduct to a drastic APOE levels reduction in neurons. Hyo Lee, Aimee J. Aylward et al. [33] have observed that stimulation and inhibition of SMAD signaling modulated APOE RNA levels in a SORL1-dependent manner. Swati Mishra, Allison Knupp et al. [34] found that the glutamate receptor subunit AMPA1 (GLUA1) and Tropomyosin-related kinase B (TRKB) is impaired by loss of SORL1. In addition, they showed that SORL1 depletion significantly affects the endosomal recycling pathway for APP and GLUA1 at double level, recycling endosome and trafficking to the cell surface. On the contrary, augmented SORL1 expression rate implements endosomal recycling for APP and GLUA1.

3.2 *ABI3*

Abelson Interactor Protein 3 Interactor family member 3 (*ABI3*), also known as NESH (new molecule including SH3) [11, 35] contains a Src homology 3 (SH3) domain, a homeobox homology domain (typical of transcription factors which guide the organism development in the embryonic age), and several proline-rich and serine-rich motifs [36]. Abi3 interacts with p21, inhibiting cell migration. In addition, its function consists in regulating actin polymerization (it is part of the abi/wave complex [37], hence resulting yet in lowered ectopic metastasis of tumor cells and cell migration [38]. Regarding brain tissue, its expression has been observed to be enriched in microglia with ramified or amoeboid morphology [39]. Here, it seems to play a role in dendritic spine morphogenesis [40]. The S209F ABI3 variant (rs616338:p.Ser209Phe) is associated to an increased AD risk [11, 35] and has been validated in Conway e al. and Sims et al. [11, 35] (secondary study). A recent study investigated about Abi3 role in AD pathogenesis exploiting modern techniques of gene expression analysis. Analysis of bulk RNAseq data confirmed the previous reported age-progressive upregulation in Abi3 levels in rodent models of AD-type amyloidosis and above all an increase in AD patients, if compared to controls. They have shown how deleting Abi3 gene meant to also delete the overlapping gene Ggnt2. Abi3-Gngt2$^{-/-}$ mice RNAseq revealed upregulation for 3 AD pathogenesis related genes, Trem2, Plcg2, and

Tyrobp (implicated for example in microglial activation), along with induction of an AD-related neurodegenerative phenotype, even in the absence of AD-typical neuropathology. Intriguingly, in APP mice, loss of Abi3-Gngt2 led to a gene dose- and age-dependent reduction in Aβ accumulation; but in Abi3-Gngt2−/− mice, it is recognizable the expression of a pro-aggregant form of human tau, which exacerbate tauopathy and astrocytosis. Thus, we could consider them contradictory effects, if we ignore the intrinsic pleiotropic nature of the genes involved in the immune response. Finally, using in vitro culture assays, they demonstrated that the AD-associated S209F mutation alters the extent of ABI3 phosphorylation. [41]

3.3 *ABCA7*

ABCA7 (ATP-Binding Cassette 7) is a membrane pump, which is required for the internalization of Aβ40 [42]. The ABCA7 gene contains 47 exons and, when translated, originates the complete transmembrane transporter protein. It is made up of 2146 amino acids with a molecular weight of 220 kDa [43]. Similarly to other ABC transporter, in ABCA7, there are two intracellular nucleotide-binding domains (NBD) with conserved Walker A and B motifs, which are necessary for ATP hydrolysis, two transmembrane domains, and two extracellular loops [43]. When cholesterol is depleted, the activation of sterol regulatory element-binding protein 2 (SREBP2) pathway led to ABCA7 expression upregulation, (inverse regulatory effect on ABCA1, the ABCA family member that has major homology level with ABCA7) [44]. Intriguingly, Abca7 depletion affected phagocytosis in mouse macrophages *in vitro* and *in vivo* [45]. As abovementzionated, ABCA7$^{-/-}$ AD mouse models presented with an increased brain amyloid acummulation (presumably through β-secretase cleavage [46]) and a lowered Aβ1-40 and Aβ1-42 oligomers uptake both in microglia and macrophages [47, 48]. In addition, a relative recent study described a putative new role for ABCA7 in AD, e.g., as a cholesterol homeostasis and Aβ efflux regulator at the level of blood–brain barrier [49]. Besides Aβ clearance, ABCA7 was also shown to directly affect Aβ production. Another research team working on Abca7 knockout mice reported a deficit in new recognition memory in males and a dysfunctional spatial reference memory in females [50], but, subsequently, impaired spatial memory was observed in a cohort of both male and female mice [50]. Abbas Dehghan, Rui Climaco Pinto et al. [51] led a metabolome-wide association study (MWAS) of AD-associated loci from GWASs exploiting untargeted metabolic profiling by ultraperformance liquid chromatography–mass spectrometry (UPLC-MS). Their results suggest how altereted ABCA7 gene expression effect on AD could be mediated by Ceramid and Sphyngolipids metabolism. First of all, they demonstrated that plasma Lactosylceramid (LacCer) concentration variations are bound to cognitive performance and whatever, at genetic level, cause modification in its expression is associated with AD risk. Then, they showed that concentrations of sphingomyelins, ceramides, and hexosylceramides were altered in Abca7 knockout mice brain tissue, in respect to wild type (WT) controls, but not in an amyloidosis mouse model. Besides, microglial activation increases intracellular level of hexosylceramides, partially via expression induction of sphingosine kinase, an enzyme, which showed a high control coefficient for sphingolipid and ceramide synthesis.

3.4 *CLU/APOJ*

Clusterin (75 to 80-kDa disulfide-linked heterodimeric all-around chaperone molecule) [52, 53] is a ubiquitous expressed protein, which was firstly known for its AD risk factor role. It is also defined Apolipoprotein J (APOJ) because of its function in lipids transport.

In humans, CLU gene localizes on chromosome 8 and has been recognized as the third LOAD risk factor gene (after APOE and BIN1), due to its contribution percentage, which is estimated at around 9% [54]. In particular conditions, Clusterin localizes intracellularly, where it is involved in signal transmission modifications. However, it is

still unclear what determines its lack of secretion. Killick et al. 2014 [55] have *in vitro* demonstrated that this change of destination is not bound to CLU mRNA levels and so probably correlates with some post-transcriptional or translation modification, such as glycosilation pattern. Anyway, although many of its functions have been identified so far, many still remain the mysteries related to its real functioning in various pathophysiological situations. For istances, starting from its abovemenzionated three main activities (chaperone, lipid transport and interference in various transduction pathways), Clusterin regulates cellular apoptosis and survival (interacting with BAX [56, 57], Ku70 [58, 59], and Cu allostasis and innate Immunity [52, 60]. Clusterin in citosol inhibits NF-κB-dependent Bcl-xl expression and thus induces arrest of the cell cycle addressing the cell to death [57, 61-64]. Acting on Aβ oligomers (from di-mers to 50-mers), Clusterin prevent their further aggregation, in order to maintain them soluble. However when Aβ burden overcomes a certain threshold, Clu stops performing its task and trapped in the plaques, exacerbates Aβ deposition [65]. In addition it mediates cholesterol (increased cellular cholesterol content can increase Aβ production [66] and changes in cellular ceramides have demonstrable effects on Aβ production and aggregation into plaques [67-69]) and Aβ efflux in CSF (cerebrospinal fluid) coadiuvated by lipoprotein receptor-related protein-2 (LRP-2) activity [70]. Human monocytes derived macrophages and mouse primary microglia triggering receptor expressed on myeloid cells 2 (TREM2) binds and takes up lipoproteins and apolipoproteins such as clusterin. Aβ endocytosis is more effective if a complex is formed between TREM2 and CLU or low-density lipoprotein (LDL) [71]. Moreover, Clusterin regulates the formation of the MAC, specifically inhibiting C5b-6, i.e., the first step in MAC formation cascade [72, 73]. McGeer et al. [74] immunohistochemistry data showed a similarities in the brain tissue clusterin and MAC staining profile, both of which localized in dystrophic neurites and neuropil threads in Alzheimer-Perusini but not in health controls, suggesting an increased clusterin levels in protective response to MAC formation. As reported by Killick et al., 2014 [55], treating neurons with Aβ generates a neurotoxic response and an associated upregulation of dickkopf 1 (DKK1), that is a well-known antagonist of canonical Wnt signaling pathway. This led to an GSK-3β upregulation, which implicated and increased tau phosphorylation rate [75] and synapse loss [76]. In CLU knockdown rat primary cortical neurons, the Aβ-driven increase in DKK1 expression is prevented and cells are protected from Aβ-induced neurotoxicity [55]. Subsequently, it was explained by the finding that Clusterin causes a switch in Wnt signaling to the non-canonical Wnt-PCP-JNK pathway, which hesitates in downstream activation of transcription factors upregulated by both Aβ and DKK1 (an upregulation prevented by CLU-Knockdown). This led to augmented levels of expression of EGR1, KLF10 and NAB2. Individually silencing EGR1 and KLF10, Aβ-induced neuronal cell death has been prevented, while silencing EGR1 and NAB2 phosphorylated tau (p-tau) have been restored down to basal unstimulated levels (EGR1 and NAB2) [55]. In AD-affected people, by positron emission tomography (PET) imaging was confirmed that elevated CLU plasma levels were positively correlated with entorhinal cortex (EC) fibrillar Aβ burden [77]. Hence the idea of exploiting it as an early and non-invasive biomarker of disease [78].

3.5 *BIN1*

Bridging Integrator-1 (*BIN1*) was originally characterized as an amphiphysin structurally related mycinteracting protein by Sakamuro et al. in 1996 [79]. BIN1 belongs to the BAR domain protein family, which are set up for membrane dynamics regulation [80, 81]. BIN1 seems to take part in several relevant pathways such as inflammation, apoptosis, and calcium homeostasis [82]. Its gene locus undergoes alternative splicing to originate various cell type-specific isoforms. All the isoforms contain two

functional domains, BAR, and the Src-homology (SH3) domains, through which regulate membrane invaginations and interactions with dynamin. Only in the neuronal isoform, there is another domain, defined as the clathrin and adaptor binding domain (CLAP) because it seems that BIN1 participates in neurons clathrin mediated endocytosis. In particular, as showed by several further studies, Bin1 is involved in dynamin recruitment to nerve terminals clathrin-coated pits [83]. Multiple genome-wide studies reported an association between BIN1 and an augmented AD risk, so much so that it is considered the second risk factor overall after APOE [84-87]. In missing BIN1-rodent cortical and hippocampal neurons endocytosis results increased and Rab5-positive early endosomes (EEs) enlarged, which culminates in endosomal membrane damage and tau loss [88]. Moreover, BIN1 Loss of BIN1 in similar cellular models also make trafficking of the type I transmembrane aspartyl protease enzyme, BACE1 (required for Aβ production) to lysosomes impaired [89]. Intriguingly, Lambert et al., 2021D reported that in human neurons BIN1 overexpression resulted in augmented EE size, while BIN1 loss in decreased EE size. Performing Targeted, quantitative RT-PCR analysis with RNA isolated from postmortem brain tissue, it was showed that BIN1 expression levels are bound to AD progression and age of onset, instead BIN1 neuronal isoforms expression were correlated with disease duration [90]. Holler et al., 2014 [91] demonstrated in post-mortem brain tissue a BIN1 neuronal isoforms downregulation in AD.

In addition, according to Sottejeau et al., 2015 [92] BIN1 protein may interact directly with Tau, although this interaction could be prevented by Tau phosphorylation. BIN1 manages the axonal sorting of BACE1, which can alter Aβ sitespecific (neuronal somatodendritic or axonal compartments) processing [93]. However, according to De Rossi et al., 2016 [80] there is no association between BIN1 with NFT and Aβ plaques and Andrew et al., [94] have shown that BIN1 expression downregulation does not regulate Aβ in 5XFAD mice. Nevertheless, AD-associated BIN1 SNPs may induce increased BIN1 microglia expression and this, in turn, could impact Tau clearance-involved chaperones expression and enanche tau release in extracellular vesicles [95]. When excitatory neurons BIN1 is genetically ablated a microglia transcriptome modulation follows, reconstructing an expression framework in which the pathways related to neuroinflammation, and reactive-oxygen species (ROS) production are strongly enhanced [96]. Is this effect mediated by exosomes? Posterity will judge.

3.6 *ADAMTS1*

ADAMTS1 (whose expression rate increases in brains affected by Alzheimer-Perusini disease) degrades several types of proteoglycans and inhibits cell proliferation, polarization and migration [97]. Therefore, if it is non-functional, it could be responsible for alterations of the extracellular matrix that no longer allow adequate control of amyloid catabolism and also for glial chemotaxis impairment. The members of the ADAMTS family are nothing more than particular ADAMs (neuronal α-secretase) with a thrombospondin motif, which would allow them to inhibit angiogenesis [98]. In light of this, the evidence that platelets also metabolise APP could represent a much more direct trait-d'union than one might think between vascular dysfunction and AD. Two recent meta-analysis [7, 99] confirm that ADAMTS1 represents a relevant actor in Alzheimer-Perusini's disease progression. Previous findings have suggested that APP probably operates as an extracellur matrix (ECM) component by means of its extracellular domain-ECM costituents interaction, likewise heparin sulfate proteoglycans and collagen [100-102]. Y. Qiu, L. Sha, et al. have recently conducted a series of experiment with the aim to elucidate ADAMTS1 function in central nervous system (CNS), both in physiological and pathological conditions [103]. For istances, we will report most relevant findings of this work. When ADAMTS1 cleaves APP at E530/L531, the resulting fragment, CTF_{ATS1} (531–695 amino acids), still contained BACE1 (also known as β-

secretase) site. However, they observed an Aβ and CTF-β (APP-derived fragment after β-secretase cleavage) reduction, which suggested that BACE1 could not further act on CTF_{ATS1}, probably because this fragment might not have accessible spatial structure for BACE1. Nevertheless, as past findings have suggested, BACE1 *in primis* degrades APP within endosomes [104, 105] and hence the APP traffiking from plasma membrane to endosomes is fundamental for its activity [106]. Considering, that according to fractionation results, APP - ADAMTS1 interaction primarily occurs on plasma membranes the APP-ADAMTS1 binding could prevent its intracellular trafficking and thus BACE1 cleavage. Nevertheless, belonging ADAMTS1 and ADAM10 to the same enzyme series (ADAM family), which is characterized by both disintegrin and zinc endopeptidases domains [107], they could act on ECM and adhesion molecules [108, 109] through comparable approcheas. Hence, these two enzymes might function in a competive way and if so, then we might see reduced α-cleavage in ADAMTS1-overexpressed situation. Y. Qiu, L. Sha et al [103] found that ADAMTS1 was clearly upregulated by Environment Enrichment (EE)-housing, which corroborated the speculation that ADAMTS1 was induced owing to neuronal firing variations involved in cognitive activities rimodulations. In addition, in the same study was showed that zif268 (an immediate-early genes (IEG) producted during cognitive encoding) induces the ADAMTS1 promoter activity. Zif268 absence severely impairs the cognitive performance in diverse behavioral tests [110].

4. Conclusions

When we talk about CNS more answers we pursuit, more question we arise. Specifically, even more difficult is dealing with CNS diseases since we have already known very little about physiologic state. If we talk about neurodegeneration, we start from a few certainties. Neurons die, synapses collapse, the connectome slowly implodes. In the background a mixed proteinopathy and abnormalities in the behavior of the innate immunity, in particular of the glial cells. Is the impaired clearance of proteins and lipids that induces pathological phenotypes in glial cells or vice versa? No doubt it is a vicious circle. The relevance of genetics in this area is expressed in altered proteins that accumulate/alter enzymes and chaperons.

These last process abnormally proteins that accumulate and altered gene products, which reprogram glial cells in an abnormal way."In this mini review we just tried to describe the better approaches at the moment in order to investigate genetic-molecular nature of neurodegenerative ilnesses and reported information about the role in AD pathogenesis of several associated genes. They were Aβ internalization, endososomal/extracellular trafficking and processment; and glial chemiotactic migration related genes. Even if we are closer to the truth today, there is still probably some way to go. In the meantime, all that remains is to continue working.

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