Review Article

Amyloid Beta Revisited: A Versatile Immune Polypeptide

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Alzheimer's disease affects about fifty million people worldwide. Its main symptoms are the formation of amyloid deposits and of neurofibrillary tangles, and cognition loss. To date, no clear etiology for this disease could be identified. I will here elaborate on the likelihood that Amyloid b is not a toxic molecule but a protective protein fragment, and that a combination of chemical and biological exposures, with metals playing a key role, are the triggering factors for Alzheimer's type dementia.

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Introduction

A vast amount of knowledge has been accumulated on neurodegeneration since the initial description of a new dementia case by Dr. Alois Alzheimer, in 1906. Most research has been interrogating the formation of the amyloid deposits and of neurofibrillary tangles from a cellular biology perspective. At the turn of the 21st century, new ideas emerged, such as a dominant role played by some viral infections, such as the Herpes Viruses[1] or the cytomegalovirus[2]. This idea was further supported by the demonstration of an antimicrobial function[3][4] of the Amyloid 1-42 peptide (later Ab), with properties similar to the diversity of antimicrobial peptides observed among living organisms[5]. Still, this hypothesis could not cover all the physiological effects and pathological configurations observed for Alzheimer's disease cases. Considering experimental data across various fields, chiefly biochemistry, for peptide-metal ion interactions, neurobiology, and also epidemiology and air pollution, I will here present a transversal and multi-causal etiology[6] for Alzheimer's disease. With respect to the existing theories, it can be viewed principally as a combination of the 'Antimicrobial hypothesis', the 'Metal Hypothesis'[7] and the 'infectious theory'[8], with some additions. It will be shown that Ab, which is generally considered as

pathogenic, is part of the immune response of the organism. This property was already considered in the antimicrobial hypothesis[9], but I will here extend its defense attributes. The main targets of this defense polypeptide are metal ions, its likely additional targets being micro-organisms. I will elaborate on the biochemical, cellular and environmental results which support this proposal.

APP and Aβ

The Amyloid Precursor Protein (APP) is an important actor in Alzheimer's disease. APP is a 770 amino-acid, membrane-embedded protein. It can be processed following two main, competing pathways: one in which lysis by α-secretase releases a non-pathogenic, sAPPα form, and one which releases the Aβ, amyloydogenic peptide. In the latter, enzyme β-secretase[10] (or BACE1) first cleaves APP into C99 (APP C-terminal) and sAPPβ, and the γ- secretase complex[11] subsequently cleaves C99 into Aβ1-42 or Aβ1-40, with other cleaved forms present in lower amounts[12]. The γ-secretase complex is a large transmembrane complex composed of Presenilin 1, Nicastrin, Anterior pharynx-defective 1 and Presenilin Enhancer 2, with Presenilin 1 exerting the actual aspartyl-protease catalytic function[11].

Various partner proteins have been shown to regulate the activity of the γ-secretase complex. These include proteins such as the Interferon-Induced Transmembrane 3 (IFITM3) protein, and Hypoxia Inducible Factor 1α HIF-1α. IFITM proteins 1, 2 and 3 are part of the innate immune system[13] and prevent the entry of various viruses, including influenza[14], coronaviruses[15] and hepatitis C[16], into the host's cells. They have been detected in CD8-T cells, B cells and NK cells[17]. They can also act as enhancers for Aβ production, by positively regulating the activity of the γ-secretase complex, as observed in mice models[18]. An IFITM3 variant has been described in patients with cognitive loss and increased Aβ accumulation (Pyun et al., 2022). Protein HIF-1a is induced under hypoxic conditions. In mice, its stimulation by provoked hypoxia has been shown to increase the enhance the activity of β- and γ-secretases, and to induce higher levels of both Aβ1-40 and Aβ1-42[19]. Proteins IFITM3 and HIF-1a can thus both induce the expression of Aβ.

The formation of Aβ has moreover been shown to be influenced by the composition of the membrane where APP is embedded[20]. Increased brain cholesterol levels indeed induce increased activities of the β- and γ-secretases, as well as an increased production of the Aβ polypeptide[21][22]. In addition, various teams could demonstrate a role for a lipid-raft localization of the APP protein and these two secretases in the production of Aβ42[23].

The above proves that the production of the Aβ polypeptide is finely regulated. Hence the idea that it is part of a natural process, not of a pathological one.

Metal ions and Aβ

Aside from its well proven antimicrobial properties[3][4][24] and an antiviral activity (Bourgade et al., 2015), the amyloid polypeptide has remarkable metal-binding properties. They are well documented for zinc, with a monomeric adduct to Aβ 1-16 structurally characterized[25]. The zinc ion is coordinated by residues His6, Glu11, and the neighboring His13 and His14 (Figure 1). This binding strongly affects the structure of the 1-16 peptide, with a disappearance of the a-helix (Figure 1). A complex of Zn2+ with two molecules of the Aβ1-16 peptide could also later be evidenced[26]. It has also been proved that Aβ interacts with copper with a high affinity, and a tendency of this adduct to self aggregate was observed[27]. A coordination to iron has also been demonstrated[28], in addition to mercury and to lead[29]. Regarding its presence in tissues, zinc could be detected over two decades ago in amygdala senile plaques, along with copper and iron[30].

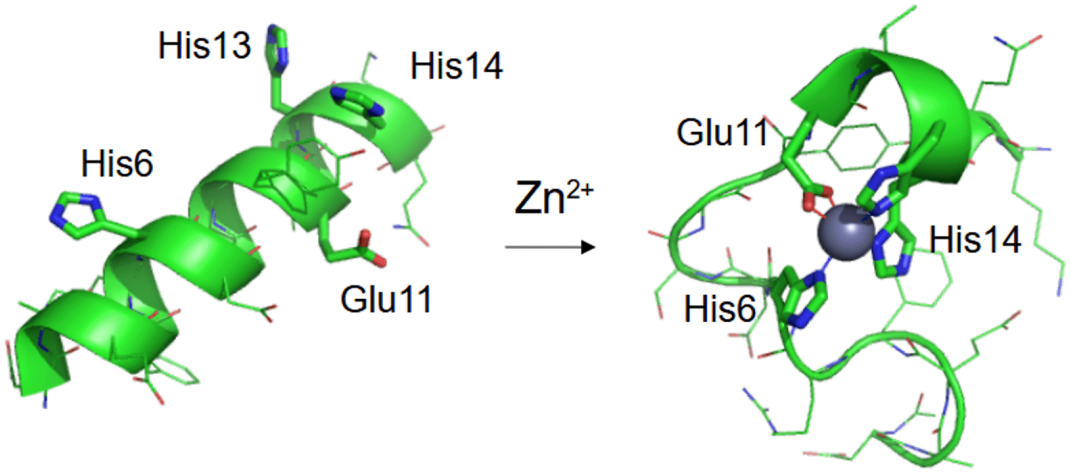

Figure 1. Change of secondary structure of Amyloid b1-16 upon metal binding. Structure on the left has been prepared based on pdb 2BP4, while the Zn-bound stucture is based on pdf 1ZE9[25].

Further cellular responses to metal exposures point towards their involvement in the development of AD. Results regarding iron, zinc and aluminium are successively presented. In HEK293 cells bearing the

Swedish APP mutations, both iron and ferritin where shown to increase the expression of the g-secretase components[31]. In neuroblastoma cells, an increased production of APP has been observed in the presence of elevated iron cellular concentrations, with a cancellation of this effect in the presence of the iron chelator desferroxiamine (Rogers et al., 2002). It was also evidenced in retina, with increased production of APP in human immortalized ARPE-19 cells exposed to ferric ammonium citrate[32]. Exposure of mice expressing APP and Presenilin 1 to high concentrations of zinc lead to an increased production of Aβ and to increased amounts of Aβ deposits in the hippocampus[33]. The cognitive performances of the animals were also affected. Regarding aluminium, rats exposed to it were shown to have increased production of Aβ both in the hippocampus and cortex[34]. These various induction experiments suggest that the production of the Aβ is influenced, if not regulated, by the presence of the metal ions.

In addition, studies on cellular cultures, animals and human cohorts have demonstrated a neurotoxical effect of metals. In human neuroglioma H4 cells and rat PC12 cells, CuO nanoparticles induced a significant apoptosis when used at concentrations above 5 µM and 25 µM, respectively[35]. In mice exposed to inhaled iron oxides nanoparticles, females showed impaired memory and increased amounts of phosphorylated tau[36]. Analyzing data of the NHANES cohort for over 4 000 patients, participants with high blood cadmium levels (>0.6 µg/L) were shown to have a 3.83-fold increased risk of AD-related death[37].

Exposure to particulate matter was moreover shown to influence the expression levels of Aβ. In cultures of mouse neuroblastoma cells exposed to nano-particulate matter for 24h, Ab was detected at concentrations twice as high as those observed in unexposed cells[38].

Finally, various studies have shown that metal chelatants can have protective effects against the accumulation of Aβ or the development of AD. In model transgenic APP2576 mice, a significant decrease in Aβ deposition was observed in aged animals (12 or 21 months) after daily administration of Zn-chelatant chlioquinol for respectively 12 or 9 weeks[39]. Thiosemicarbazones are well-described copper chelators. Incubating SH-SY5Y cells with a thiosemicarbazone coupled to a stilbene moiety reduced the amounts of Aβ aggregates detected, both in the absence and in the presence of added CuCl2[40]. Another example for a role of zinc chelation is provided by a quite fascinating peptide, humanin. First identified as protective against AD[41], its P3S mutant was recently detected in ApoE4-carrying centenarians, thus

indicating its highly protective role against AD[42]. Its wild-type form was later shown to bind zinc[43]. These results suggest its function could be to assist Aβ in its defensive role against metal accumulation.

All these pieces of information, put side by side, suggest a re-interpretation of the role of metals and Aβ, and of their interplay, in neurodegeneration. The observed cases of lethality or toxicity described in cellular studies should be attributed, in my opinion, not to Aβ itself, but to the metal-Aβ agglomerates. These large aggregates, unlike the 'oligomer' size aggregate[44], cannot be gotten rid off by microglia. In addition, they are not composed only of the Aβ polypeptide, as many of the above-mentioned experiments have considered, but of Aβ chelated by metal ions. And it is the metal ions which the immune system is intending to get rid off, not the Aβ.

It is hence here proposed that the physiological deposition of Aβ as plaques or deposits is linked to a metal-enriched environment. In the absence of metal ions, or under concentrations sufficiently low to be regulated by other metal-binding proteins, such as S100A6[45] or S100B[46], Aβ is released within the cell at low levels. It possibly plays housekeeping functions, or exerts its antibiotic role thanks through its dominantly a-helix structure (see Infections, below). In the presence of excess metal ions, Zn most likely, but also Cu or Fe, the production of Aβ would increase in order to chelate them. The resulting metal-Aβ complex has a strong propensity for self-aggregation, as described for Zn[26]. Moderate metal concentrations would thus lead to the 'oligomers' observed by various groups. These can be processed and eliminated by microglia, under a TREM2-dependent chemotaxis (see below; [47][48]), and with elimination of the metal ions. TREM2 (Triggering Receptor Expressed on Myeloid cells 2) variants that favor the proper removal of oligomers would thus be beneficial. When exposed to EDTA, the oligomers separate, and Aβ can re-enter the fibrillization pathway (which is pathogenic), as observed on neuroblastoma N2a cells[49]. In the experiments by Cristóvão and coworkers, protein S100B similarly plays the role of a Zn-chelating agent with respect to the oligomer (Cristóvão et al., 2020); the Aβ having lost their coordinated zinc lose their propensity for self-aggregation, return to an a-helix form, and can anew play their defensive role.

Regarding the elimination of the metal ions during the phagocytosis process of the oligomers by microglia, it is most likely realized by metallothioneins. Metallothioneins are 6-to-7 kDa proteins with an elevated proportion of Cys residues. They have a strong ability for binding metals, which they coordinate through two separate Cys-rich domains[50]. They have been shown to bind Cd2+, Zn2+, Ag+ and Cu+

(Khatai et al., 2004). Regarding their expression, they are mainly secreted by astrocytes, and have also been suggested to be secreted by microglia in rats (Agullo et al., 1998).

When the concentrations of Aβ-compatible metals increase, or when facing certain oxidating or toxic species, such as particle-born ferrous oxides, cuprous oxides[51] or cadmium, the Ab-dependent defense would be overwhelmed, and the polypeptide-metal adducts would start to accumulate. Plaques, which cannot be processed by microglia, would start to form, owing to the self-aggregation propensity of the metal-Aβ adducts. This process would be aggravated by oxidative stress processes, such as those induced by the presence of NOx species or excessive NO amounts. In addition, these aggregates contain various peptide-bound metal ions. While zinc is not redox active, copper can catalyze various oxidation and oxygenation reactions when incorporated at protein active sites[52][53]. Iron is an equally important source of radical species, when bound to proteins or peptides[54]. In addition, the Aβ-Cu and Aβ-Fe adducts have been shown to be responsible for Fenton-like reactions[55], which release highly reactive radical species (Xiao et al., 2025). These aggregates would thus be a source of radical species within the cell, which could attack protein residues and oxidize membrane lipids.

Relation to ApoE

Another actor for this immune reply is protein ApoE, an important constituent of brain apolipoproteins. It carries cholesterol from the liver or digestive tract to the cells, or from cells to the liver for its elimination, and has been involved in immune signaling[56]. Variants of ApoE have been described as the strongest risk factor for the development of Alzheimer's dementia. In humans, three main isoforms have been described for this protein, with respective frequencies of approximately 78% for E3 (Cys112-Arg 158), 14% for E4 (Arg112-Arg158) and 8% for E2 (Cys112-Cys158)[57]. Immunodetection on AD patient brains showed that the accumulation of Aβ plaque was dependent on the apoE genotype of the patient, with more Aβ deposits in carriers of the ε4 allele[58]. This trend can be related to the propensity of each ApoE isoform to interact with peptide Aβ1-42, with a stronger interaction evidenced for the ApoeE2 and ApoE3 isoforms[59], as well as to the trafficking of Aβ to lysozomes[49].

Keeping in mind that the main function of Ab is to bind metals, and that is also serves in the protection against infections, let's consider, first, the number of Cys residues present in each ApoE isoforms, second, the fact that some more ancestral populations bear the e4 allele, and third, the implication of a VCAM1-ApoE-TREM2 recognition in the removal of oligomers by microglia[60].

The microglial protein TREM2 has been shown to play diverse roles in the trafficking of Aβ, being both involved in the chemotaxis of microglia[47] and in the degradation of Aβ oligomers by microglia[48]. Recent studies on mice thus evidenced a VCAM1- and ApoE- dependent microglia chemotaxis towards Aβ oligomers, leading to their clearance[60]. Additionally, some main mutants have been identified for TREM2, which induce a higher risk to develop AD. Though signaling through protein Spleen Tyrosine Kinase (SYK) was shown to be necessary for the removal of Aβ oligomers by microglia, the Arg47His variant of TREM2 was shown not to activate this pathway (Wang, Sudan et al., 2022). It was also shown to interact with Aβ oligomers more weakly than the wild-type form[61], similar to the Arg62His variant. These two properties overall favor an accumulation of Aβ.

The His157Tyr variant, first identified among Han Chinese[62], was later shown to increase the risk of AD more than 3.5 times over a broader cohort[63]. The effect of this mutation can be understood by the higher shedding rate of the mutant with respect to wild-type TREM2[64], while a complete TREM2 is required to induce phagocytosis[65] and hence, the clearance of Aβ deposits. These results concur with the increased amounts of shedded TREM2 (N-terminal fragment) detected in the CSF of AD patients[66] (Haslegrave et al., 2016).

Considering all the above, one sensible interpretation is that ApoE acts as a companion to Aβ, in addition to playing the role of a communication hub with microglia, through TREM2. Regarding its variants, ApoE4 mainly assists the anti-microbial activity of Aβ, through the identified antimicrobial peptide identified in its 133-150 positions (Pane et al., 2016), while the e2 and e3 variants assist its metal-binding activity through their Cys residues (respectively x2 and x1). Their long a-helices would thus wrap around the Aβ oligomers, which carry metal ions, and cargo the oligomers to microglia for phagocytosis[67]. These dual roles most likely originate in evolutionary pressures.

The above scheme is supported by the improved clearance of oligomers observed in PDAPP/TRE mice expressing the e2 and e3 variants, relative to those expressing e4 (Castellano et al., 2011). This interaction pattern also matches the relative kinetics observed for the aggregation of labeled Aβ to ApoE, with aggregation speeds of Aβ increasing from ApoE2 to ApoE3 to ApoE4[68]. It is also compatible with the results obtained on direct interactions between ApoE and Ab 1-40 using a gel-shift assay[69].

The role of infections

An important point of focus in the recent dementia literature is an involvement of the immune system in the development of Alzheimer's disease and of dementia. Multiple studies could establish a link between viral and bacterial infections on the one hand, and the development of dementia on the other hand, as already reviewed[70][71]. This has been the case for the Herpes Simplex Virus[72] (HSV; Letenneur et al., 2008), cytomegalovirus[73], varicella zoster virus[74] (VZV), Zika virus[75], for bacteria such as Chlamydophila pneumoniae (Bu et al., 2015) and Porphyromonas gingivalis[76]. Diverging results were obtained concerning Toxoplasma gondii, depending on ethnicity[77][78]. Co-infections were also shown to increase the risk of dementia and cognitive decline, as observed for HSV and VZV in a Korean cohort[74], for VZV, and over a more diverse list of infections[79].

On another token, various studies could demonstrate a positive effect of vaccinations on the progression of dementia. This was e.g. observed for varicella-zoster virus[80][81], influenza (Levine et al., 2023), pneumonia[82] and Bacillus Calmette-Guérin[83] vaccinations. Moreover, an association of vaccines more markedly decreased the risk of developing dementia as single vaccinations, as observed with the zoster and Tdap vaccines[84] and with the shingles and respiratory syncitial virus vaccines[85].

These results clearly emphasize the relationship between neurodegeneration and infections, or an individual's history of immune exposure. And they can be explained under the current perspective, taking into consideration the fact that the Aβ polypeptide is part of the immune system. In the case of micro-organisms, the provoked defenses could involve B and T cells, NK cells, the IFITM proteins, and possibly the Aβ polypeptide itself.

Regarding HSV and CMV at least, the T-cell defenses are barely relevant. HSV expresses an immediate early protein, ICP47, which inhibits its recognition by T cells[86], while CMV expresses two proteins with similar functions, US3 and US11[87].

NK cells are important actors in the defenses against cancer cells and against micro-organisms. They can attack their targets without the need for a prior exposition, through the recognition of general phenotypes, such as the down-regulation of the major histocompatibility complex class 1. Micro-organisms which are targeted by them include the herpes-type viruses HSV, HZV, CMV and EBV, as well as some fungi[88]. Still, these viruses have evolved mechanisms to evade attack by the immune system, as already described for HSV[89], among VZV carriers (Campbell et al., 2018) and among EBV and CMV co-

carriers (Müller-Durovic et al., 2019). Since these latter two viruses have high prevalence rates among the general population[90][91], such resistance issues are not to be disregarded. Deprived NK defenses would be most frequent among the individuals with an existing herpes-type infection: the successive infecting virus would benefit from the weakening of NK cells provoked by the previous infection. A second line of defense is the IFITM proteins, IFITM 1, 2 and 3. They intervene on the cytosolic side of the lipid membrane to prevent the entry of various viruses[92], as described above.

The overall picture would thus be that the entry of viruses such as HSV, VZV, EBV and CMV would provoke, in the majority of individuals, whose NK cells are little effective against those viruses, an increase in IFITM3 and Aβ. Be metals present at high concentrations in the cell, such that the existing metal defense processes (S100 and existing Aβ) cannot cope with them, the structure of the Aβ produced would be altered, resulting in its metal-bound folding, which would prevent its interaction with the envelope of the viruses (see Figure 1). It is hence the combination of weakened NK-cells (due to virus evasion processes mainly, since no consensus exists regarding an aging of these cells) and the presence of metals, which would render the neural cells susceptible to these viral attacks (Figure 2). Cholesterol concentration would here play an ambivalent role, since both assisting the entry of the viruses[93], and provoking an increase in the amount of Aβ produced to assist defense against metals. The mechanism proposed here at the molecular level corresponds to that recently described at the population level with exposure to traffic-based air pollution[94].

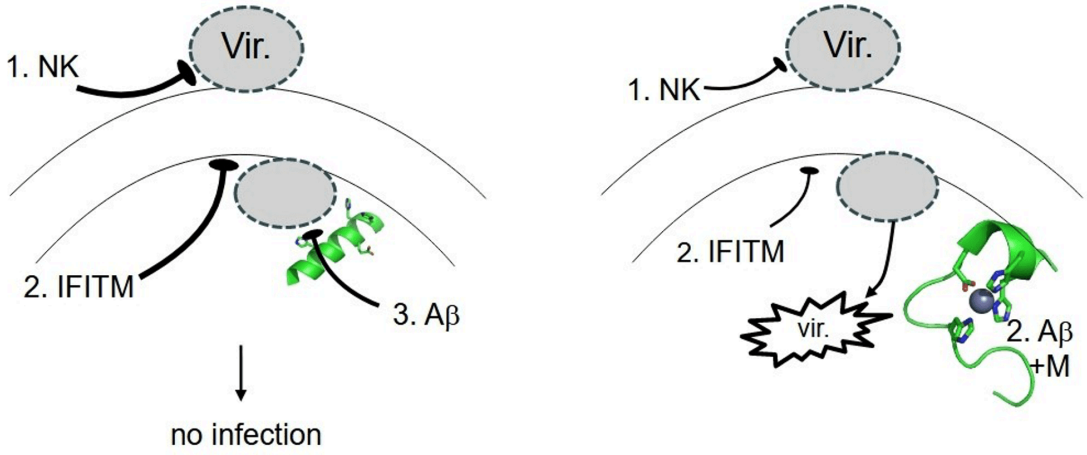

Figure 2. Virus attack on a neuron. NK cells are the first line of defense. IFITMs prevent virus entry. Ab, when not metal-bound (left), interacts with the virus and cargoes it for elimination. Its metal-bound folding (right) strongly reduces its anti-microbial properties, and would let the virus in the cell in case of weakened NK-cells (see text) and IFITM defenses.

Conclusion

Overall, it appears that the development of Alzheimer's disease is related to the accumulation of metals or metal-bearing particles in the brain. The Amyloid β polypeptide, demonstrated as a good zinc- and copper-chelating molecule by many groups, is thus not a toxic species, but a protective one, as already hinted at[95]. It is both involved in the defense against excessive metal concentrations, and against micro-organisms, and is assisted in this role by ApoE.

The present proposal for the regulation and role of Aβ addresses the classical dual option a researcher faces, in life sciences, when observing that a protein or a peptide is over-expressed in a given physiological condition: is this protein or peptide provoking the pathological condition, or is the body replying to another threat (which the researcher does not have under focus) through this over-expression?

Further population-based studies are for now warranted in order to determine whether the critical exposure to metals or particulate matter occurs across one's lifetime, or if the most critical period is early development, as often considered in epidemiological studies on contaminants. A paradigm shift to

introduce more chemical considerations in Alzheimer-oriented studies needs to happen in order to address the relevant questions, and obtain clinically-relevant answers.

Statements and Declarations

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Conflicts of Interest

None declared.

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