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. Metal ions have been shown to accumulate in amyloid deposits. Moreover, multiple infections have been shown to be risk factors for the development of Alzheimer's and other dementia, with vaccines playing protective roles. I will here elaborate on the likelihood that Amyloid b is not a toxic molecule, but a protective protein fragment, targeted both against infections and metals. A combination of chemical and biological exposures, with metals playing a key role, would thus be key factors in the triggering of Alzheimer's disease.

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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 (or BACE1;[10]) 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[19]. 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[20]. 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[21]. Increased brain cholesterol levels indeed induce increased activities of the β- and γ-secretases, as well as an increased production of the Aβ polypeptide[22][23]. 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[24].

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. Its interactions with metals ions on the one hand and, on the other hand, the cellular responses to increased metal concentrations, both further demonstrate this regulation.

Metal ions and Aβ

Aside from its well proven antimicrobial properties[3][4][25] and an antiviral activity [26], the amyloid polypeptide has remarkable metal-binding properties. They are well documented for zinc, with a monomeric adduct to Aβ 1-16 structurally characterized by NMR[27]. In this structure, 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 fold upon binding (Figure 1, right). A complex of Zn2+ with two molecules of the Aβ1-16 peptide could also be evidenced[28]. A dimeric coordination of Zn2+ by Aβ1-40 could also be evidenced by EXAFS, with Cu2+ evidencing only monomeric coordination[29]. In addition, Aβ-bound Zn2+ ions have been detected as a possible source of Zn2+ ions for APP, thus inhibiting its ferroxidase activity through a metal exchange[30]. 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[31], in contradiction to the results described above with Aβ1-40. A coordination to iron has also been demonstrated[32], in addition to mercury and to lead[33]. Existing model studies can be misleading, owing to the different aggregation propensities of Aβ40 and Aβ42[34] and their different solubilities, as well as the interactions of Aβ with membrane lipids.

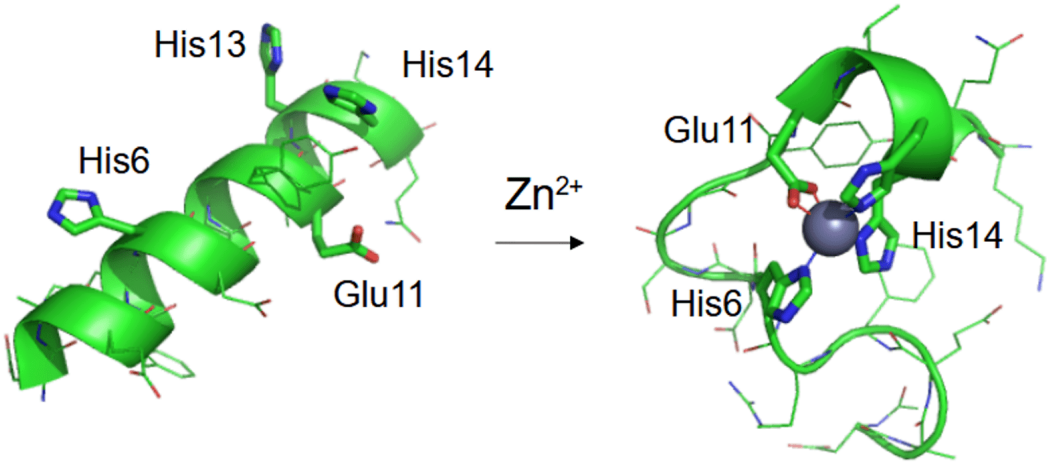

Figure 1. Change of secondary structure of Amyloid b1-16 upon metal binding. Structure on the left has been prepared based on pdb 2BP4, while the Zn-bound stucture is based on pdf 1ZE9[27].

Zinc has moreover been shown to accumulate in the brain tissues of AD patients. Such an accumulation could be observed in the plaques present in the brains of AD patients, with no equivalent detection in age-matched, non-demented subjects[35]. It could also be detected in amygdala senile plaques, along with copper and iron[36]. In another study, in the cortex of AD patients, zinc was detected at levels more than double those present in control patients, with the levels of amyloid increasing along with those of detected zinc[37]. In APP-/- mice, iron was shown to accumulate in various organs, including brain and liver, with increases of +26% and +31% respectively under a normal diet, compared to age-matched controls, and increases of +13% and +90%, after a temporary high-iron diet[30]. Cerebral cortex (+40%) and liver (+80%) were also the organs in which copper was shown to accumulate in APP-/- mice[38].

Further cellular responses to metal exposures point towards their involvement in the development of AD. Results regarding iron, zinc and aluminium are presented. In HEK293 cells bearing the Swedish APP mutations, both iron and ferritin where shown to increase the expression of the g-secretase components[39]. 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[40]. It was also evidenced in retina, with increased production of APP in human immortalized ARPE-19 cells exposed to ferric ammonium citrate[41]. 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[42]. 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[43]. 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[44]. In mice exposed to inhaled iron oxides nanoparticles, females showed impaired memory and increased amounts of phosphorylated tau[45]. 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[46].

Exposure to particulate matter (PM), which often contains metals (see last section), 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[47]. PM can also influence cognition, as observed in 4-week old mice submitted to PM2.5 aspiration[48]

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 clioquinol for respectively 12 or 9 weeks[49]. 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[50]. Another example for a role of zinc chelation is provided by a quite fascinating peptide, humanin. First identified as protective against AD[51], its P3S mutant was recently detected in ApoE4-carrying centenarians, thus indicating its highly protective role against AD[52]. Its wild-type form was later shown to bind zinc[53]. 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 their relation to Aβ in the development of Alzheimer's disease. 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[54], 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[55] or S100B[56], Aβ is released within the cell at low levels. It plays housekeeping functions, binding the metals present at low concentrations in a non-pathogenic manner, 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, Fe, Cd, Al or Hg, the production of Aβ would increase in order to chelate them. This induced production is supported by the various cell-based studies listed above. The production of Aβ in metal-enriched cells would produce a complex, which has a strong propensity for self-aggregation, as described for Zn[28] and Cu[31].

Moderate metal concentrations would lead to the 'oligomers' observed by various groups. These can be processed by microglia (Figure 2), under a TREM2-dependent chemotaxis[57][58] (see below), and with a separation of Aβ from the metal ions. TREM2 (Triggering Receptor Expressed on Myeloid cells 2) variants that favor the proper removal of oligomers would thus be beneficial against these Aβ-metal oligomers.

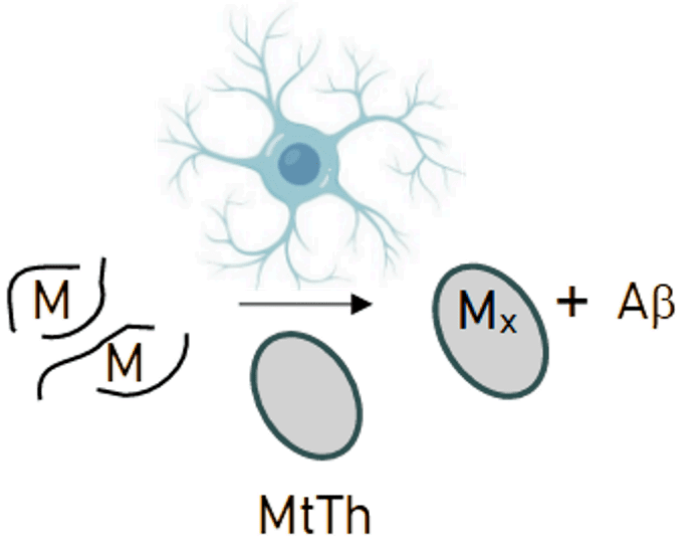

Figure 2. Processing of Ab oligomers by microglia. M designates a metal ion, MtTh metallothionein III. Ab polypeptides are processed by lysosomes or recycling endosomes.

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The elimination of the metal ions during the phagocytosis of the oligomers by microglia is most likely performed by metallothioneins. Metallothioneins (MtTh) 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[59]. They have been shown to bind toxic metals such as As and Cd[60][61], and more physiological metals such as Zn2+ and Cu+[62], with Cd and Zn simultaneously evidenced e.g. in MtTh from rabbit liver[63]. Regarding their expression, they are mainly secreted by astrocytes, and have also been suggested to be secreted by microglia in rats[64]. In addition, MtTh-III has been shown to be involved in Alzheimer's disease, as protecting neurons from Aβ[65]. and being down-regulated among AD patients, at least those of Japanese ascent[66]. MtTh-III has also been shown to exchange metal ions with Aβ-metal adducts, Zn7-MtTh3 being capable of swaping Zn ions with Cu-Aβ[67]. This protein hence is altogether a good candidate for the capture of metal ions from Aβ oliogmers, prior to their degradation or to the recycling of metal-free Aβ.

When the concentrations of Aβ-compatible metals increase, or when facing certain oxidating or toxic species, such as particle-born ferrous oxides, cuprous oxides[68] 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[69][70]. Iron is an equally important source of radical species, when bound to proteins or peptides[71]. In addition, the Aβ-Cu and Aβ-Fe adducts have been shown to be responsible for Fenton-like reactions[72], which release highly reactive radical species[73]. 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[74]. 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)[75]. 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[76]. 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 ApoE2 and ApoE3 isoforms[77], as well as to the trafficking of Aβ to lysozomes[78].

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 implication of a VCAM1-ApoE-TREM2 recognition in the removal of oligomers by microglia[79], second, the fact that some more ancestral populations bear the e4 allele, and third, the number of Cys residues present in each ApoE isoforms along with the evidences that ApoE interacts with metal ions[80].

The microglial protein TREM2 has been shown to play diverse roles in the trafficking of Aβ, being both involved in the chemotaxis of microglia[57] and in the degradation of Aβ oligomers by microglia[58]. Recent studies on mice thus evidenced a VCAM1- and ApoE- dependent microglia chemotaxis towards Aβ oligomers, leading to their clearance[79]. 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[81]. It was also shown to interact with Aβ oligomers more weakly than the wild-type form[82], similar to the Arg62His variant. These two properties overall favor an accumulation of Aβ.

The His157Tyr variant, first identified among Han Chinese[83], was later shown to increase the risk of AD more than 3.5 times over a broader cohort[84]. The effect of this mutation can be understood by the higher shedding rate of the mutant with respect to wild-type TREM2[85], while a complete TREM2 is required to induce phagocytosis[86] 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[87].

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[88], while the e2 and e3 variants assist its metal-binding activity through their Cys residues (respectively x2 and x1), and possibly Met64 and Met108, located near Cys112

(PDB structure 1BZ4). Their long a-helices would thus wrap around the Aβ oligomers, which carry metal ions, and cargo the oligomers to microglia for phagocytosis[89]. 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[90]. 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[91]. It is also compatible with the results obtained on direct interactions between ApoE and Ab 1-40 using a gel-shift assay[92].

Origin of the metal overload

If the main function of the Aβ polypeptide is to eliminate metal ions, where could those responsible for an overload of this elimination pathways come from? As often seen in biology, most likely from multiple sources, as depending on each one's exposure profiles and metabolism. Hence no 'number 1' cause is for now identifiable, except if considering a specific sub-population.

The likely origins for the metal overload can be divided into two main domains: the `inside' (the organism itself) and the `outside' (intake). Regarding the former, metal concentrations could be released within the cell owing to cellular dysfunctions. These could be related to aging phenomena, as well as to oxidation phenomena, as detailed below.

One possible major metal release source within the cells are metallothioneins. Metallothioneins have been shown to be good metal chelatants, as described above. In addition, metallothioneins can release metals after reaction with H2O2[93] or with NO under limited glutathione[62]. Increase in the oxidative status of the cell, due among other to mitochondrial aging or leaks[94][95], could thus provoke the release of their multiple metal ions. With the subsequent accumulation of radical-generating Aβ-Fe or -Cu adducts, those neurons would hence enter a vicious oxidative cycle.

Another possible source for metal accumulation is a decrease in the function of Zn transporters (ZnT). Members of the SLC30 family of tranporters decrease intracellular zinc concentrations[96]. In healthy cells, ZnT1 expels Zn ions from the cytoplasm, while ZnT2 uptakes them into endosomes, and ZnT3 is involved in their vesicular uptake. The expression levels of ZnT3 have been shown to decrease with age in mice[97], while the amounts of its mRNA are decreased in AD brains[98]. In addition, ZnT3 has been shown to be regulated by sex hormones, with estrogen enhancing its expression in mouse brain[99] and

an influence of mice gender observed on zinc amounts and plaque deposition[100]. Overall, aging and/or age-related decrease in sex hormones would thus induce a lesser capture of cellular zinc into vesicles, and enhance the likelihood of a Zn overload within cells, favoring Zn-Aβ oligomers and aggregates. Owing to the differences in sex hormone regulations between men and women, and to the involvement of Zn in the formation of amyloid aggregates, the age- and hormone-dependent regulation of ZnT3 could help understand gender differences in the prevalence of AD.

Regarding the exposure-based accumulation, it can stem from various routes. Intaken foods and drinks are a possible source, as described in the case of copper in drinking water[101]. Metals can also stem from inhaled air, as borne by metal-carrying nanoparticles and increased by traffic-based pollution. Amid 50-300 nm nanoparticles collected in the air of Mexico City in March 2006, Pb was present in 28% of the nanoparticles, Hg in 21% and Fe in 44% of them, being frequently associated with Mn and Zn[102]. Metals can also stem from inhaled tobacco smoke, as observed in settled house dust for Cd[103].

Amyloid, metals and 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[104][105]. This has been the case for the Herpes Simplex Virus[106][107] (HSV), cytomegalovirus[108], varicella zoster virus[109] (VZV), Zika virus[110], for bacteria such as Chlamydophila pneumoniae[111] and Porphyromonas gingivalis[112]. Diverging results were obtained concerning Toxoplasma gondii, depending on ethnicity[113][114]. Co-infections were also shown to increase the risk of dementia and cognitive decline, as observed for HSV and VZV in a Korean cohort[109], for VZV, and over a more diverse list of infections[115].

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[116][117], influenza[118], pneumonia[119] and Bacillus Calmette-Guérin[120] 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[121] and with the shingles and respiratory syncitial virus vaccines[122].

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[123], while CMV expresses two proteins with similar functions, US3 and US11[124]. The other herpes-type viruses possibly possess similar early T-cell antagonists. In addition, T cells undergo aging and senescence phenomena[125][126]. Naive T-cells become less abundant with aging, repeated infections or auto-immune conditions, the response to new infections thus being strongly diminished[127][128].

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[129]. Still, these viruses have evolved mechanisms to evade attack by the immune system, as already described for HSV[130], among VZV carriers[131] and among EBV and CMV co-carriers[132]. Since these latter two viruses have high prevalence rates among the general population[133][134], 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[135], 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 proteins and existing Aβ) cannot cope with them, the structure of the Aβ produced would be altered, resulting in its metal-bound folding (see Figure 1). Under this fold, the interaction of Aβ with the envelope of viruses is prevented. 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 3). Cholesterol concentration would here play an ambivalent role, since both assisting the entry of the

viruses[136], 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[137].

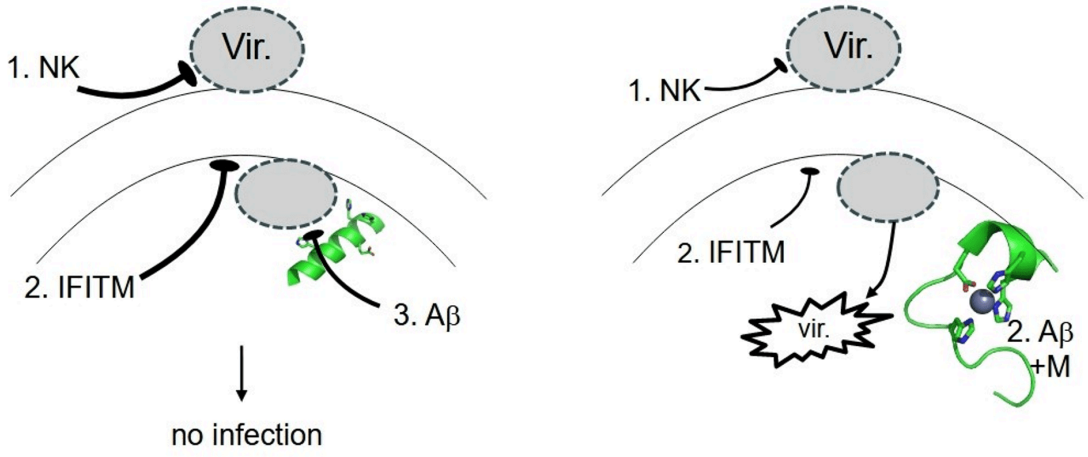

Figure 3. Virus attack on a neuron. NK cells are the first line of defense. IFITMs prevent virus entry. Ab, when not metal-bound (left), interacts with the virus and cargoes it for elimination. Its metal-bound folding (right) strongly reduces its anti-microbial properties, and would let the virus in the cell in case of weakened NK-cells (see text) and IFITM defenses.

Conclusions

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[138]. It is both involved in the defense against excessive metal concentrations, and against micro-organisms[9], 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, when physiological defenses are not fully present yet, as already observed in epidemiological studies. A paradigm shift to introduce more chemical considerations in Alzheimer-oriented studies would help address more disease progression-relevant questions, and obtain clinically-relevant answers.

Statements and Declarations

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Potential Competing Interests

No potential competing interests to declare.

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