Neurodegeneration: Potential Causes, Prevention, and Future Treatment Options

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Here I advance a hypothesis that neurodegeneration is a natural process associated with aging due to the loss of genetic redundancy following a mathematical model $R(t) = R_0(1-\alpha e^{(\beta C+\gamma I+\delta E t)t})$, where the calorie intake (C) and immune response (I) play critical roles. The early onset of neurodegenerative diseases such as Alzheimer's disease is due to metabolic imbalance or chronic immune reactions to various infections. Therefore, the potential treatment options for neurodegenerative diseases are to modulate metabolism and immune response.

Age related neurological disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) exert tremendous social and economic strain on society. The World Alzheimer Report 2010 estimated that worldwide economic cost of age-related dementia is over $600 billion annually, and predicted it will rise rapidly in the near future. Even though scientific research in academic and industrial settings has made significant progress in understanding the basis of neurodegeneration, the development of disease-modifying treatment options lags behind. The majority of treatments in development for AD funded by public and private sources are based on the β-amyloid cascade hypothesis[1, 2]. However, late-stage clinical trials based on this hypothesis have not been successful, such as Semagacestat (bace 1 inhibitor)[3, 4] from Eli Lilly and earlier immunotherapy from Elan Pharmaceuticals[5]. In addition, there are hundreds of current clinical studies targeting the same pathway by reduction of β-amyloid load or its accumulation. This begs the critical question: will the reduction of β-amyloid burdens result in the slowing-down of neurodegeneration? Here we propose a novel hypothesis regarding the cause of neurodegeneration which implies alterative treatment options. It is imperative for society as a whole to pool resources to solve the urgent needs of an aging worldwide population. Therefore, where and how to use the limited resource becomes an increasingly important question.

HYPOTHESIS

Aging is the result of the reduction of genetic redundancy due to accumulated cellular damage from free radicals. These free radicals come from two main sources, metabolic process and immune response, as well as a secondary source, the environment.

The proposed mechanism of DNA damage is especially true for neurons, since differentiated cells do not replicate or undergo replication repair and the genetic errors cannot come from DNA replication. In addition, the implied reduction in genetic redundancy not only originates from direct DNA damage, but also comes from damage to other cellular components, as this damage can reduce cell's ability or accuracy to transcribe or translate the genetic information. Two major sources of free radicals, metabolism[6] (mitochondria respiration) and immune response[7] are unavoidable and therefore, life is destined to age.

Combining this hypothesis with the free radical theory of aging[8], the reliability theory of aging[9, 10] and the Gompertz-Makeham[11, 12] law of mortality, we can arrive at a mathematic equation of neuronal aging:

$$R(t) = R_0(1-\alpha e^{(\beta C+\gamma I+\delta E t)t})$$

R(t): redundancy at time t; R_0, initial redundancy; α, frequency of redundancy loss by free radical hits; β, free radical index of calories; C, amount of calorie; γ, free radical index from immune responses; I, quantitative immune response; δ, environmental impact index; E, quantitative environmental impact; t, time.

We have two copies of each chromosome; therefore, the initial redundancy (R_0) for females is close to 2 and for males, it is close to 1.95. The loss of redundancy in males is due to the loss of genes in Y chromosome during evolution. Even though we have not elucidated the various constants and the time factors for calorie intake and the immune response, the implications of this mathematical model are not diminished. In majority of individuals, the impact from calorie intake and immune response dominate and the environmental factors are hard to quantify. However, the environmental impact can dominate in extreme cases because of the time factor (Et), such as via repeated head trauma or prolonged exposure to heavy metals. Similarly, positive environmental factors can provide added protection, giving some individuals with extraordinary life expectancies and sharp mental acuity late in life. In addition, the weight distribution between calorie impact and immune response varies with time as well. Most likely the immune responses increase impact as we age. Figure 1 illustrates the aging curve assuming an average environmental impact (E=0). Currently we do not know when the onset of the disease begins ($R_{(t)}$ equals 1.5 or 1.0?). However, 16% reduction of the combined impact from caloric and immune response throughout life could delay the onset of age-related dementia by more than a decade (Fig.1).

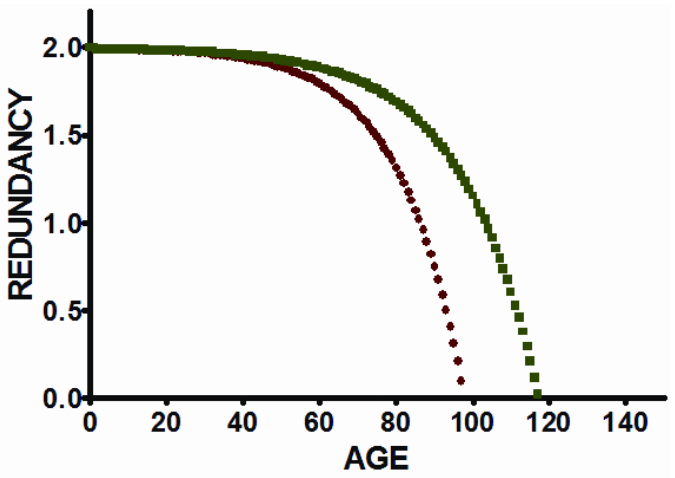

Fig. 1. Reduction of calorie and immune esponse can slow down neurodegeneration. Hypothetical plots of the redundancy decline with equation $R(t) = 2(1-0.003e^{0.06t})$ (red) and $R(t) = 2(1-0.003e^{0.05t})$ (green).

The initial redundancy differences between male and female do not result in significant differences in neuronal aging rate late in life (Fig.2). However, because women have longer life expectancies in developed countries, they might be more susceptible to developing AD. On the other hand, the initial redundancy differences between sexes are large enough to make males more susceptible to environmental factors early in life.

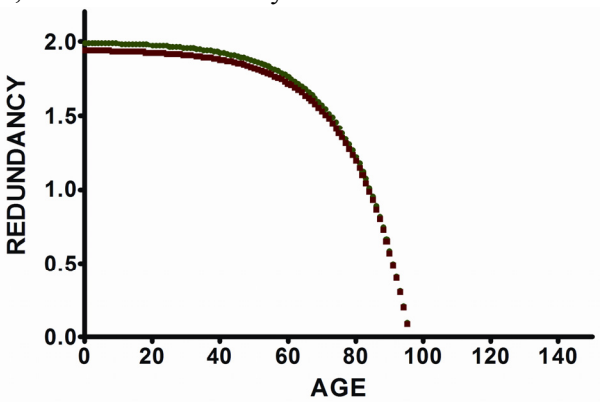

Fig. 2. Initial redundancy differences between male and female do not result in significant differences in the redundancy decline later in life. Hypothetical equation plotted with $R(t) = 2(1-0.003e^{0.06t})$ (green) and $R(t) = 1.95(1-0.003e^{0.06t})$ (red).

POTENTIAL CAUSES OF ALZHEIMER'S DISEASE

The β-amyloid cascade theory has dominated the research and development field in Alzheimer's disease for the last two decades, although scientists have begun to be aware of the metabolic connection, especially the connection between type II diabetes and Alzheimer's disease[13]. Then what are the causes of Alzheimer's disease? Our hypothesis would suggest that AD is intricately associated with age and one can suggest that AD is almost unavoidable if an individual lives long enough. Then why do some individuals get the disease earlier? Our theory suggests that there are two possible causes of Alzheimer's disease besides those rare cases due to genetic mutations.

Majority of cases are the results of metabolic disorders. From the equation $R(t) = R_0(1-\alpha e^{(\beta C+\gamma I+\delta Et)t})$, the metabolic term has two factors. The amount of calorie (C) plays the most important role, as an increased calorie intake will inevitably increase the free radical production. The free radical index (β) of calorie includes the quality of calorie and the balance of calorie sources (carbohydrates, proteins and fat). The metabolism of carbohydrates is the

preferred energy source for neurons, as glycolysis can generate energy (ATP) without producing free radicals, whereas the metabolism of proteins and fatty acids can only be accomplished through mitochondria oxidation. Therefore, diet with high fat content will cause increased rates of neuronal aging. Consequently, majority of cases of Alzheimer's most likely arise from the imbalance between glycolysis and mitochondria oxidative phosphorylation due to dietary imbalance throughout life. In addition, the free radical index of calorie could vary among individuals due to genetic variations and life-style differences.

Some cases could be the results of chronic infection, especially from these pathogens that can infiltrate the central nervous system (CNS), as these infections elicit persistent immune responses. This aspect still requires further research about what types of pathogens can penetrate the relative immune privilege of the CNS[14]. Some chronic infections caused by prions[15], bacteria such as *Borrelia burgdorferi* (Lyme disease)[16-18], or viruses such as Herpes simplex virus[19] can infiltrate the brain and elicit persistent immune reactions. These cases could possibly be treated with antiviral or antibacterial agents if diagnosed early enough. The connection of AD with other immunological disorders, such as autoimmune diseases, still requires further investigation.

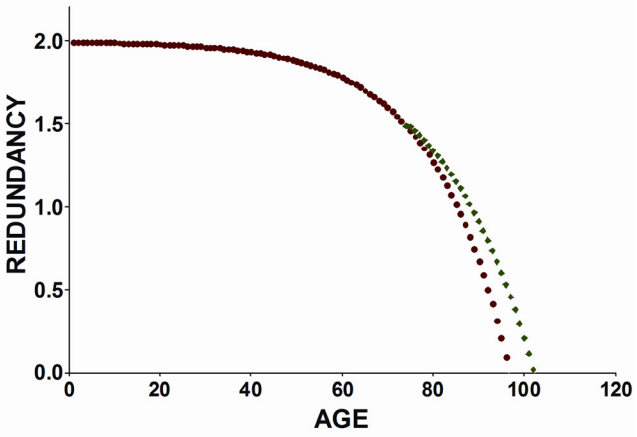

Fig. 3. Reduction of calorie or immune impact by 16% (green line) upon diagnosis could delay disease onset by about 3 years

TREATMENT OPTIONS

Our hypothesis has profound implications in the development of disease modifying treatment options. The key to slowdown neurodegeneration is to reduce the production of free radicals either from modulation of immune responses or mitochondria respiration or the combination of both. The mathematical model can provide some guideline for the design of treatment strategies. Let's assume that the onset of AD is the result of reduction of redundancy to 1.0 and the symptoms appear when the redundancy is at 1.5. If we start treatments that reduce the combined impact of calorie and immune response by 16%, we could delay the disease onset by about three years (Fig.3). How far can we delay the disease onset exactly remains to be seen. However, it is possible to delay the disease for a decade if we can start the optimized treatment regime early enough, which put a premium on the early diagnosis. Figure 4 illustrates the importance of early diagnosis and treatment. The theoretical model assumes that the treatment reduces the free radical impact by 33% ($R(t) = 2(1-0.003e^{0.06t})$ in comparison with $R(t) = 2(1-0.003e^{0.04t})$). Starting treatment at $R_{(t)}$ value of 1.75 or 1.5 makes a significant difference (Fig.4).

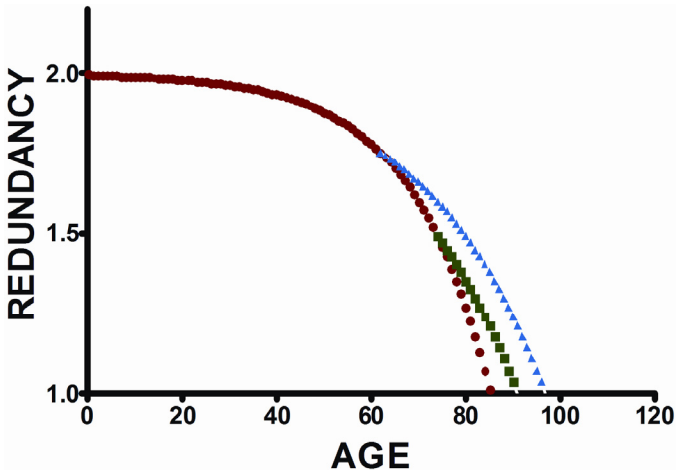

Fig. 4 Early diagnosis and treatment initiation are critical to delay the onset of disease. Starting treatment at R(t) of 1.75 (blue line) or 1.5 (green line) makes significant difference

A: Immune Modulation.

Dietary restrictions are generally difficult to adhere to for physicians as well as for patients. However, immune modulation has been used successfully for the treatment of various diseases such as arthritis, Crohn's disease, organ transplantation and others[20]. These medications have a relatively good safety profiles and should be explored for the treatment of Alzheimer's diseases. Recent development of monoclonal antibodies for the modulation of immune responses is

especially interesting, since they have defined targets, an established safety profile and characterized mechanism of action. We project that monoclonal antibodies against TNF alpha or beta, IL-1, IL-2, IL-6, and IL-12 should all have significant activities towards treating Alzheimer's disease. Small molecule immune modulators could have the desired therapeutic value as well. Inhibitors in the TNF-alpha pathway, immune suppressants (currently used in transplantation), estriol, and even moderate concentrations of steroids could also exhibit disease modifying activities. We project that optimal immune modulation can delay the onset of AD by three to five years. It is imperative that clinical trials be conducted as soon as possible for these novel approaches.

Undoubtedly, immune suppression will have significant side effects, such as increased risk of cancer and various infections. However, the benefit most likely is much greater than the risk, especially since many immune modulators have been in clinical applications for a significant period of time.

B. Metabolism Modulation

Effective small molecule metabolism regulators have not been discovered. The targets for slowing down neuronal aging are two-fold. The first option is to slowdown mitochondria activity, especially neuronal mitochondria activity, without depleting energy supply to neurons. The second option is to facilitate the neuronal glycolysis. Evidently, these goals are difficult to achieve, as they could be contradictory at times. Here we would like to suggest a number of targets for the development of future therapeutic options.

Mitochondria activity regulators.

Many enzymes regulate mitochondria metabolite flow. The critical requirement is to regulate mitochondria activity without the accumulation of the reactive intermediate metabolites that can generate free radicals, such as semiquinones. One possible option is to restrict the supply of ubiquinone by limiting its biosynthesis. The human enzyme COQ7 (*c* elegans clk-1 homolog) could be an interesting target as it is required for the synthesis of ubiquinone[21]. However, development of inhibitors for this enzyme is a difficult task, as robust inhibition could lead to many diseases, even neurodegeneration, as it could limit the energy supply to neurons. The ideal inhibitor would be a non-competitive inhibitor (hopefully reducing the V_{max} by 25 to 50%) without changing the affinity for its substrate. The other option would be to increase the mitochondria activity for non-neuronal cells, as these cells can metabolize the non-carbohydrate and glycolysis metabolites from neurons. The combination could facilitate neurons to generate more of their energy from glycolysis. Aside from exercise, few other options can reach this goal.

Another possible option is to regulate the free iron concentration in neurons, because Clk-1 homologs all require iron for activity. However, it is a challenge to limit iron concentrations in neurons alone.
Most importantly, our hypothesis suggests that popular supplements such as coenzyme Q10 which could facilitate the mitochondria phosphorylation oxidation will not have any positive effect on neurodegeneration. On the contrary, it most likely has an adverse effect if there are any.

Glycolysis Facilitators

The goal is to facilitate the neurons using glycolysis as the major energy source without limiting the amount of energy produced. Glycolysis in the cytosol is a self-limiting process as it depends on the conversion of NADH back to NAD+ through mitochondria or other oxidation reactions to restart glycolysis. Normally neurons can carry through the oxidation of glucose to generate ATP both in the cytosol and from mitochondria. However, an excess amount of ketone bodies from circulation taken up by the neurons will inhibit the glycolytic process. An ideal compound can facilitate the conversion of NADH to NAD+ in the cytosol without generating free radicals. Molecules such as thionine derivatives could potentially accomplish such a task. In addition, thionine derivatives such as methylene blue can also accelerate the mitochondria electron transport reactions without generating semiquinones, which are a source of free radicals[22]. Therefore, it is not a surprise that methylene blue showed some promise in a phase 2 trial for treating Alzheimer's disease[23-25]. However, methylene blue is less than ideal,

as it can bind many reductases as well as DNA. Further research is required for the identification of more ideal compounds.

Many compounds in development aiming to restore the balance of glycolysis and mitochondria phosphorylation oxidation for treating type II diabetes could have therapeutic value in Alzheimer's disease as well, such as GKA activators, amylin analogs, and leptin analogs[26]. There are also many compounds in development to treat obesity by regulating calorie intake. All these approaches will impact the developing course of Alzheimer's disease as well.

PREVENTION

Our hypothesis that Alzheimer's disease is mainly a metabolic disorder implies that it is preventable. The health benefits of a balanced low calorie diet are multifaceted. It not only reduces cardiovascular diseases and type II diabetes, but it is also the best option for preventing Alzheimer's disease. A balanced diet low in fat and protein not only delays aging in general, but also impedes neuronal aging and development of AD.

Physical exercise also plays an important role in preventing neurodegeneration. The preferred energy source for neurons is glucose. However, neuronal glycolysis depends on the uptake of glucose and continued efflux of its metabolites. Overdependence of the whole body on fatty acid metabolism will impede the neuronal use of glycolysis, as the circulating ketone bodies will supply neurons with excess nutrients. Furthermore, excess energy supply will down-regulate the expression of glucose transporters on all organs, which further impedes glucose uptake of all cell types. On the other hand, exercise will burn the excess calories and promote the expression of glucose transporters in all cell types. In addition, exercise will strengthen the non-neuronal organs and promote blood flow. The efflux of metabolites (most likely lactate)[27] from glycolysis in neurons can be facilitated by improved circulation, and these metabolites can be used for energy by other organs such as a strong heart and increased muscle mass[28, 29], which in turn will help the neurons to generate more energy from glycolysis.
Maintaining an active life style by incorporating exercise and a sensible diet will go a long way to maintain one's mental edge.

FUNCTIONS OF PROTEINS INVOLVED IN NEURODEGENERATION

Alzheimer's Disease

A number of genes whose mutation can cause early onset of Alzheimer's disease or Parkinson's disease have been identified. In the case of Alzheimer's disease, three genes coding for protein β-amyloid precursor protein (β-APP), presenilin 1 and presenilin 2 have been identified to cause early disease onset when there are deleterious mutations[30]. Extensive research on these proteins has reported various functions. Those identified functions mostly revolve around the production of amyloid peptides whose aggregation could result in the formation of plaques, the hallmark of Alzheimer's disease. Then how will the functions of β-amyloid fit into our hypothesis? Currently, only one target protein has been firmly established to interact with β-amyloid-ABAD (**a**myloid **b**eta-peptide-binding **a**lcohol **d**ehydrogenase)[31]. ABAD is a mitochondria protein involved in the metabolism of short-chain fatty acid and displays a diversified substrate specificity[32]. It can oxidize a variety of 17-β-hydroxysteroids and plays a role in steroid metabolism. Therefore, β-amyloid peptide has at least two functions:

1. Inhibiting the oxidation of fatty acid metabolites, which would slowdown the mitochondria oxidative phosphorylation reactions.
2. Suppressing the immune response. Through binding to ABAD, β-amyloid peptide will inhibit the oxidation of steroid derivatives, which can suppress the immune response. The existence of amyloid peptides in the central nervous system could thus contribute to the immune privilege of the brain as well.

Therefore, the production of amyloid peptides is the response of the central nervous system to reduce the production of free radicals from the mitochondria and the immune response. However, genetic mutations resulting in the continuous over-production of β-amyloid peptides will impede neuronal cell's ability to generate enough ATP and thus result in early neuronal death.

This hypothesis suggests that the current clinical trials that focus on the reduction of β-amyloid peptide production most likely will not work, except perhaps in rare genetic cases. We may observe an initial symptom relief by limiting the production or increasing the clearance of amyloid peptides due to increased temporary ATP production. However, the prolonged exposure to these treatments most likely exacerbates the neurodegeneration process and causes brain inflammation due to loss of immune modulation by β-amyloid peptides.
The other gene that is involved in the increased risk of development of Alzheimer's disease is apoE isoform of apolipoproteins. Our hypothesis is consistent with the current research demonstrating that apoE is most likely involved in fatty acid metabolism and immune modulation[30].

Parkinson's disease

Parkinson's disease is the result of degeneration of dopaminergic neurons in the substantia nigra pars compacta of the brain, which results in the decreased production of dopamine[33-35]. In comparison with Alzheimer's disease, PD involves the early degeneration of a specific region of the brain instead of the global degeneration of the neurons for AD. There are also significant similarities at later stages between both diseases[36, 37]. However, these differences imply a more significant genetic role for PD pathogenesis, contrary to the current belief that majority of PD cases are sporadic. Our hypothesis suggest that majority of cases of PD are associated with genetic variations, whereas only a fraction of cases are due to the environmental factors. This implies that future genetic approaches for the treatment of PD are feasible, whereas genetic interventions for AD are not very likely to succeed.

Mutations of many genes can cause early onset of Parkinson's disease[38-40]. These genes code for proteins α-synuclein, DJ-1, Parkin, pink1, Lrrk2, UCHL1, ATP13A2, Nurr1, and HtrA2. The reported and proposed functions of these proteins vary significantly in the literature and consistent integration of these functions is lacking. Our hypothesis proposes an integrated pathway for all the park proteins. Collectively, Park proteins are involved in the regulation of three functions: mitochondria function, oxidative stress sensing, and immune modulation. Recent research on the functions of these proteins supports our hypothesis that these proteins are involved in regulating mitochondria function[41], though evidence to link these proteins to immune regulation is still lacking. However, the recent genome wide association studies linking immune proteins to PD[42] lend further support to our hypothesis.

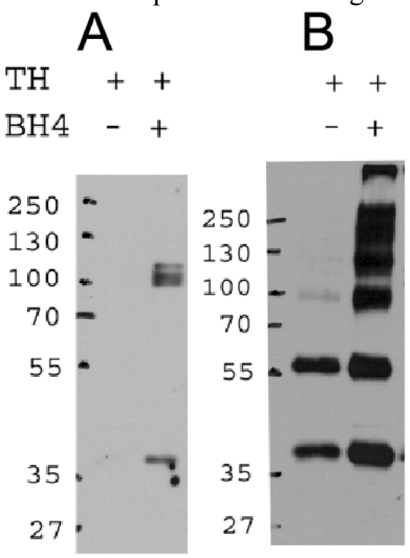

Fig. 5. TH induced aggregation of α-synuclein**.** α-Synuclein was mixed with TH in HEPES, pH 7.0 buffer and incubated at 37°C with shaking (210 rpm) in the absence of reduced glutathione and the resulting samples were analyzed by SDS-PAGE. Alpha-synuclein was detected by western blot with anti-synuclein monoclonal antibody (syn211). A, total reaction mixture; B, 30,000 x g pellet; the reaction mixtures were centrifuged at 30,000g at 4°C and the pellets were washed three times with 1xPBS buffer.

MECHANISM OF PROTEIN AGGREGATION

Oxidation of biomolecules by reactive oxygen species during aging will give rise to ketones, epoxides, and quinones. These moieties are strong electrophiles that can react with nucleophiles such as amino groups and sulfhydryl groups to form cross-linked proteins. Therefore, the formation of protein aggregates is a normal cellular process of aging. Normally, these proteins are cleared by the proteasome as they form, thus establishing a homeostasis. However, proteasome degradation of aberrant proteins requires ATP, which would exacerbate the energy requirement under oxidative stress. Under oxidative stress, cells such as neurons will slow down the mitochondria respiration to reduce the free radical production. At the same time, the proteasome requires additional ATP to degrade damaged proteins. These contradictions are resolved through the precipitation of damaged proteins to form tangles or plaques. However, the protein precipitation process requires an initiator. We suspect that a number of proteins act as such initiators, including α-

synuclein, β-amyloid peptide, tau, and parkin. Of these proteins, α-synuclein plays the most important role, as it can initiate protein aggregation when its C-terminal tyrosine residues are oxidized to catechols by hydroxylases, such as tyrosine hydroxylase, phenylalanine hydroxylase, and possibly tryptophan hydroxylase. The aggregation of α-synuclein induced by tyrosine hydroxylase is shown in Fig. 5.

The tendency of catechol-containing proteins to crosslink is used by many species to form plaques or glues for attachment[43]. One interesting observation of the α-synuclein C-terminal sequence is its surprising similarity with the repeating sequence of mussel protein Dpfp1 (Fig.6). The tyrosine residues in Dpfp1 are hydroxylated to exert its cross-linking abilities for the formation of plaques[44]. In fact, purified Dpfp proteins from mussels spontaneously form high molecular weight aggregates[45]. It is interesting to note that Mpfp1 (also called Mefp1), like α-synuclein, has little defined secondary structure *in vitro*[46].

Therefore, the formation of protein tangles or plaques is a way to reduce energy expenditure by neurons. The process is similar to the formation of neuromelanin and melanin, as both pigments originate from catechols. Functionally, protein tangles and plaques also share similarities with neuromelanin. They are strong metal chelators, especially of ferrous and ferric ions, to sequester them from cytosol. Overall, instead of serving as initiators of neurodegeneration, we believe that the formation of protein tangles and plaques are the results of a protective mechanism in response to persistent oxidative stress.

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Dpfp1           K P G P Y D Y D G P Y D K
A-synuclein Y E M P S E E G Y Q D - Y E P E A
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Fig. 6. Sequence alignment of the repeating sequence of mussel protein Dpfp1 with α-synuclein.

CONCLUDING REMARKS

Despite herculean efforts from researchers across academics and industry, the cure for AD has been elusive. In fact, clinical trials based on the β-amyloid hypothesis have not been successful so far. It is time to try alternative hypotheses and adopt different approaches for the development of AD treatment options. The hypothesis that neurodegeneration originates from metabolic imbalance or overactive immune system is supported by numerous studies including epidemiology studies showing[47, 48]that patients with type II diabetes display increased risk of AD. The recent genome wide association studies also identified that cholesterol metabolism and immune system are implicated in the etiology of AD[49, 50]. Taking together, adjustments to development plans are warranted, especially for the pharmaceutical industry that invests heavily in the advancement for AD treatments.

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