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Antimicrobial Amyloid-β: The Antagonistic Pleiotropy between Innate Immunity and Alzheimer's Disease

by Emma Healy

Abstract

Alzheimer's disease is a medical issue of global importance, affecting millions of individuals each year. From an evolutionary perspective, the persistence of a trait associated with such detrimental impacts on fitness must be explained. Although past research has considered it an inevitable byproduct of aging, the current prevailing hypothesis is that Alzheimer's is the consequence of an evolutionary trade-off. Multiple genes and phenotypic traits can be considered the drivers of this trade-off with Alzheimer's, but this review focuses on one well-supported relationship: the association between inflammation and neurodegenerative diseases. Specifically, we will analyze new data on the antimicrobial properties of amyloid-β, exploring how the functional similarities—and potential evolutionary relationships—between amyloids and antimicrobial peptides maintain selection for Alzheimer's.

Keywords: Alzheimer's, amyloid-β, antimicrobial peptide, antagonistic pleiotropy, cost of defense, innate immunity, inflammation

Introduction

In November of 1901, Auguste Deter was checked into a mental asylum in Frankfurt, Germany. She "presented with ideas of jealousy toward her husband, a rapidly worsening memory weakness and pronounced psychosocial impairment; sometimes she felt that someone

wanted to kill her and began to shout wildly" (Cipriani et al., 2011). Auguste died a few years later, but her physiatrist, Aloysius Alzheimer, was particularly affected by her case and continued to study the abnormal neuronal disease. In 1907, he published the first paper describing the histopathological features of a disease that would later be named after him.

Now, Alzheimer's disease is the most common cause of dementia, currently affecting 5.4 million Americans (Alzheimer's Association [AA], 2016). One in nine Americans over the age of 65 has Alzheimer's, and almost one in three Americans over the age of 85 is afflicted (AA, 2016). The disease is devastating: a leading cause of death among the elderly that is associated with debilitating symptoms and an insurmountable financial burden. Patients often undergo symptoms similar to those of Auguste Deter, such as memory loss, confusion, increased anxiety, decreased judgment, and personality changes (AA, 2016). Financially, Alzheimer's is a burden upon both families and government programs: healthcare and hospice costs for Alzheimer's patients are expected to amount to $236 billion in 2016 (AA, 2016).

Alzheimer's disease is a critical and recognized health issue. As of November 2016, there were 470 ongoing clinical trials,[1] as well as numerous wet-lab studies, in the United States. Because of the complexity of the disease, a variety of physiological pathways and drugs are research targets. Two pathological proteins involved in Alzheimer's, amyloid and tau, are perhaps the most extensively researched biomolecules. These extensive investigations into the biological origins and mechanisms of Alzheimer's disease have enabled the development of important treatments; moreover, they lay the foundation to expand our understanding of Alzheimer's beyond its pathophysiological mechanisms. We are now beginning to investigate the inflammatory features associated with Alzheimer's and their evolutionary consequences.

[1] Number obtained by searching a registry of clinical trials (ClinicalTrials.gov) for open studies that include the term "Alzheimer."

The role of evolution in shaping Alzheimer's has been largely overlooked, with the exception of a handful of publications (Glass & Arnold, 2012; Bufill et al., 2013) . Among these reviews, the innate inflammatory response is only briefly discussed as a driver of selection. In fact, since 1996—when Finch and Marchalonis first speculated that amyloid plaques evolved from certain ancestral mechanisms of inflammation—research on the topic has been scarce. Meanwhile, abundant research has demonstrated the role of inflammation in Alzheimer's but omitted the evolutionary perspective (Akiyama et al., 2000). This review seeks to combine the two research perspectives to provide evidence for an evolutionary trade-off between inflammation and neurodegenerative diseases such as Alzheimer's. We will explore the costs and benefits associated with this trade-off by examining the potential neurotoxic and antimicrobial properties of amyloid-β. In addition, we will touch upon the evolutionary origins of the relevant genes and discuss the potential ramifications of the proposed hypothesis for the clinical treatment of Alzheimer's.

Alzheimer's from the Evolutionary Perspective

Certain fundamental concepts in evolutionary medicine can be applied to the persistence of Alzheimer's. In particular, we will discuss trade-offs—beneficial traits that are associated with costs—and how they relate to system vulnerabilities. Trade-offs can be viewed from multiple perspectives: genetic, physiological, developmental, or behavioral. A trade-off must have a genetic basis to produce an evolutionary consequence, however, exploring trade-offs from other perspectives is often worthwhile since the relevant traits are frequently genetically controlled, and phenotypes may be easier to research than genotypes. From the genetic perspective, past studies have discussed specific alleles as they relate to Alzheimer's pathology; for example, Glass and Arnold (2012) explored selection pressures on the ancestral apolipoprotein E (*APOE*)

allele, for which the *APOE4* allele is a known risk factor for Alzheimer's. While we will touch upon the genetic foundation for amyloid-β formation—specifically the role of the amyloid precursor protein (*APP*) gene—we will focus primarily on physiological trade-offs.

Two types of trade-offs are particularly important to our discussion of Alzheimer's: antagonistic pleiotropies and costs of defense. An antagonistic pleiotropy—first identified by George Williams in 1957—describes a phenomenon where one gene controls multiple traits that affect fitness oppositely at different stages in life. Pleiotropies often manifest as fitness benefits early in life that are associated with costs later in life because the young within a population are more likely to reproduce than the elderly, thus selection—which acts to maximize reproductive fitness—is strongest upon traits that appear in early life. Investigating Alzheimer's as a consequence of an antagonistic pleiotropy is valid, as its detrimental effects are often not realized until an advanced age: 81% of Alzheimer's patients are at least 75 years old (AA, 2016).

Alzheimer's may also be considered an exaggerated cost of defense. In evolutionary biology, researchers agree that evolution tolerates large fitness costs if they are associated with large benefits, especially if a system is crucial to survival or reproduction. A growing body of research on inflammation and Alzheimer's suggests that the disease may be a cost of the innate immune system. However, identifying the mechanistic processes that control this relationship has been difficult since the complete pathophysiological pathway behind Alzheimer's is not yet understood. Multiple interactions are likely involved in the association, but this review will focus primarily on the immunological role of amyloid-β plaques.

Recent studies indicate that amyloid-β plaques have antimicrobial properties, demonstrating a potential function for these otherwise pathological proteins (Kumar et al., 2016). While this attribute may only be a component of the evolutionary history of Alzheimer's, its

contribution to natural selection deserves to be evaluated. We will examine research supporting the notion that neurodegenerative amyloid-β plaques form as an exaggerated cost of defense—a cost that is tolerated because the proteins' antimicrobial properties also contribute to improved fitness in an antagonistic pleiotropy.

The Neurotoxicity of Amyloid-β Plaques

Alzheimer's is a neurodegenerative disease, associated with neuron death and atrophy within Alzheimer's-specific regions of the cerebral cortex, the outer layer of brain tissue responsible for a variety of critical functions. At a molecular level, its pathophysiology is complex and heavily debated, but the presence of neurofibrillary tangles—insoluble aggregates of tau proteins—and amyloid-β plaques in the brains of Alzheimer's patients is well documented. The prevalent hypothesis for why Alzheimer's occurs—the "amyloid cascade hypothesis"—asserts that toxic amyloid-β peptides accumulate, affecting downstream biochemical and neurological processes and causing neuronal dysfunction.

Amyloids, in general, are self-assembled, degradation-resistant aggregates of protein fibrils whose substructure consists of cross-β-sheets. (The β-sheet is a twisted, pleated sheet of amino acids connected through hydrogen bonds and is a common secondary structure in proteins. The cross-β-sheet is particular to amyloid-like fibrils and consists of a double β-sheet). Amyloids are often associated with a disruption of normal physiological function, but functional forms do exist in nature. In the case of Alzheimer's, enzymes called secretases cleave APP—a large and functional precursor protein—to form amyloid-β peptide fragments (Kumar et al., 2015). These amyloid-β peptides aggregate to form both small, soluble oligomers and larger, insoluble plaques. Researchers have explored the neurotoxicity of both forms of amyloid-β, and their findings are inconclusive. While past studies emphasized the pathological consequences of

insoluble plaques, recent research hypothesizes that soluble oligomers are more toxic than the insoluble plaques, perhaps because of their increased mobility (Hardy & Higgins, 1992; Haass et al., 2007). Regardless, both biomolecules result from the same pathway of aggregation and since amyloid-β plaques are more easily detected, they are often used as an indicator of neurotoxic activity. The mechanisms through which amyloid-β functions are poorly understood; however, research has associated it with an accumulation of neurofibrillary tangles, a disruption of mitochondrial function, and an interference with intracellular calcium signaling—all of which may participate in neurodegeneration (Swerdlow, 2007; Bloom, 2014; Mossmann et al., 2014; Demuro et al., 2010).

While the majority of research considers amyloid-β plaques to be an instigator in Alzheimer's pathology, skeptics argue that amyloid-β plaques' neurotoxicity has not been definitively proven (Hardy 2009). One critique is that current research does not definitively demonstrate whether amyloid-β plaques contribute to or result from Alzheimer's symptoms. Thus, an alternate hypothesis postulates that amyloid-β is a product of pathogenic events, rather than an initiator (Lee et al., 2007). A more nuanced critique warns that the role of amyloid-β, while involved, may be limited and combined with a variety of other contributing factors (Pimplikar, 2009; Small & Duff, 2008). Specifically, Brier et al. (2016) speculate that the neurofibrillary tangles formed by tau proteins are more closely associated with the pathophysiology of Alzheimer's.

These perspectives are worth considering, as this review focuses solely on amyloid-β; however, the amyloid cascade hypothesis is the current basis for most Alzheimer's research, and few alternative hypotheses have been explored in depth. Furthermore, multiple studies into the disease's clinical presentation, genetic risk factors, and biochemical basis all support the

amyloid-hypothesis (Hardy & Selkoe 2002; Selkoe & Hardy, 2016). Thus, amyloid-β plaques and oligomers are a relevant focus as we explore evolutionary trade-offs.

Inflammation and Neurodegeneration

A connection between inflammation and Alzheimer's pathology has been speculated for decades—since Ishii et al. detected antibodies within plaques from the brains of Alzheimer's patients in 1975. Since then, a surge of published research, from animal models of infection to clinical studies with anti-inflammatory drugs, has corroborated the initial discovery (Mawanda & Wallace, 2012). For example, in an epidemiological study, exposure to viral and bacterial pathogens was found to be significantly associated with Alzheimer's (Bu et al., 2015). Another study found that human β-defensins, a type of antimicrobial peptide, are expressed more in the brains of Alzheimer's patients than in controls (Williams et al., 2013). A review by Miklossy (2011) found that spirochetes (helical, gram-negative bacteria) were discovered eight times more frequently in Alzheimer's patients than in controls.

Standing alone, these outcomes are inconclusive: they do not demonstrate whether infection precedes or follows neural damage. Although the relationship is still ambiguous, additional studies have suggested a causal relationship by reproducing the hallmarks of Alzheimer's with an initial infection. Miklossy et al. (2004) exposed rodent neural and glial cells to *B. burgdorferi*, a bacterium that causes Lyme disease, and observed increased levels of amyloid precursor protein (APP) and amyloid-β deposits. After infecting mice with *Bordetella pertussis*, the bacterium that causes whooping cough, McManus et al. (2014) found an increase in glial cell activation and an accumulation of amyloid-β. Similar results were discovered for viral infections: exposure to HSV-1 stimulated amyloid-β production in neuronal cell cultures (Bourgade 2015). With increasing evidence for the causal role of inflammation in Alzheimer's,

researchers are delving into the associated mechanisms, only to discover that Alzheimer's inflammatory processes are remarkably complex.

The potential mechanisms contributing to the central nervous system (CNS) immune response, and their consequential effects on neuron health, are diverse. Reviews on the subject have cited the role of microglia, inflammatory cytokines, and inflammasomes in Alzheimer's pathogenesis. Microglia are cells located in the brain and spinal cord that control the CNS innate immune response. Their excess activation and "priming," an alteration of their function based on prior infections, may contribute to aging and cognitive decline (Hoeijmakers et al. 2016). Additionally, abnormal levels of inflammatory cytokines, secreted proteins that either promote (pro-inflammatory) or inhibit inflammation (anti-inflammatory), may contribute to Alzheimer's pathology (Lio et al. 2003; Zheng et al. 2016). Consequentially, researchers are also exploring the role of inflammasomes, the protein oligomers that promote the maturation of inflammatory cytokines (Olsen & Singhrao 2016). These mechanisms are not exclusive, and together, in response to infections, they may trigger neuroinflammation and neuronal death, as well as an accumulation of amyloid-β. In fact, multiple facets of the immune response can be linked to amyloid-β production. In particular, microglia—which can be stimulated by inflammatory cytokines or T-cells that have infiltrated the brain—appear to produce amyloid-β (Bitting et al., 1996; Lynch, 2013).

The relationship between inflammation and amyloid-β production has been well researched in the context of Alzheimer's pathology, but most research has focused on the nature of the relationship, without questioning why it exists from an evolutionary perspective. Research has only recently begun to emphasize the functional role of amyloid-β in the CNS immune response, a topic that may have important ramifications for our evolutionary understanding of the

disease. If amyloid-β peptides contribute to the CNS immune response, the fitness benefits associated with their immunological function may be the foundation for an important trade-off—explaining why evolution has tolerated the detrimental effects of amyloid-β on cognition. To fully explore this topic, however, we must examine more than the selection pressures that have ensured the continued prevalence of Alzheimer's in our population: we must also explore the evolutionary origins of APP and amyloid-β.

Evolutionary Origins and Conservation of APP

Before determining why Alzheimer's has persisted in our population, it is useful to consider how it originated. Protein sequences prone to aggregation are prevalent across species and have been conserved throughout evolution (Sanchez de Groot, 2012). A wide range of species use amyloid aggregates for a diverse set of biological functions. For example, organisms use amyloids as biological structural components, to facilitate cellular adhesion, or to mediate cell-to-cell signaling (Fowler, 2007; Pham & Sunde, 2014). Humans may use amyloids to stop bleeding after injuries and even as a template to produce melanin (Fowler, 2007). Since protein aggregates can be toxic, mechanisms have evolved to reduce proteins' affinity for aggregating, especially in biologically crucial proteins; however, organisms can also utilize this toxicity as a defense mechanism against microorganisms. These functional roles of protein aggregates may underlie the selection pressures on specific protein domains; furthermore, the precursor protein to amyloid-β itself has encountered notable evolutionary selection.

APP is an ancient gene with a long evolutionary history. Tharp and Sarkar (2013) constructed a phylogenetic tree of the *APP* gene family, discovering that the ancestral *APP* gene arose approximately 600 million years ago during the Ediacaran period. Within that gene, the protein domain capable of forming amyloid aggregates likely evolved 450 million years ago,

during the Ordovician Period, and has since been highly conserved (Tharp & Sarkar, 2013). Notably, the secretases involved in cleaving APP (α-, β- and γ-secretases) have also been highly conserved (Shariati & Strooper, 2013). It is unclear whether APP and these secretases first evolved as a beneficial adaptation or as a spandrel—a byproduct of selection on another trait. However, the conservation of APP and its homologues, amyloid precursor-like proteins (APLPs), suggests that these proteins have since acquired functional significance and undergone positive selection.

APP is necessary for the viability of multiple species. In *C. elegans*, knockout of an *APP*-related gene, *apl-1*, can result in developmental defects and death; in *Drosophila,* silencing of *APPL* (an *APP* ortholog) causes defects in neuronal migration and patterning; and in mice, a deficit of certain APP alleles can generate postnatal growth deficits or death (Hornsten et al., 2007; Cassar et al., 2016, Heber et al., 2000). APP is clearly an essential protein in many organisms, and it appears to be multifunctional. Studies have found roles for APP (and its product amyloid-β) in neuronal development, cellular adhesion, neurotransmission, cholesterol transport, and innate immunity (Coulson et al., 2000; Yao & Papadopoulos, 2002; Puzzo et al., 2008; Spitzer et al., 2016).

The apparent necessity of these functions reinforces the theory that an antagonistic pleiotropy contributes to Alzheimer's, since for humans, any benefits associated with APP coincide with a risk of disease later in life. From an evolutionary perspective, the role of amyloid-β in innate immunity is particularly interesting, since it also frames Alzheimer's as an evolved cost of defense. The theory is supported by research demonstrating that amyloid-β protects against fungal, bacterial, and viral infections in multiple models.

The Antimicrobial Properties of Amyloid-β

A collection of recent *in vivo* and *in vitro* studies has demonstrated the antimicrobial properties of amyloid peptides. In 2010, Soscia et al. postulated that amyloid-β was an antimicrobial peptide, citing its similarities to other antimicrobial peptides and testing it against microorganisms. Their discovery was the first to suggest that the immune system responds to CNS infections by producing amyloid-β because of its function, rather than as an unintentional byproduct. They measured the antimicrobial properties of amyloid-β *in vitro* against twelve common pathogens and found that it was effective against eight of them—including the bacterium that causes meningitis and the fungus most often responsible for neurocandidiasis, a fungal infection of the CNS (Soscia et al., 2010). They tested the *in vivo* abilities of amyloid-β by observing the antimicrobial properties of homogenates of the human temporal lobes—a region of the brain where the concentration of amyloid-β tends to be high—from Alzheimer's patients and controls (Soscia et al., 2010). Alzheimer's homogenates were 24% more active against the fungus *C. albicans* than control homogenates (Soscia et al., 2010).

In 2016, Kumar and Spitzer expanded the field of research on the antibiotic and antifungal properties of amyloid-β. Kumar et al. (2016) discovered that expression of amyloid-β protected mice, nematodes, and cell cultures against infections and increased survival rates. Spitzer et al. (2016) tested the antimicrobial activities of amyloid-β variants of different lengths, discovering that certain variants ($A\beta_{x\text{-}42}$) successfully attacked all tested pathogens. Interestingly, these antimicrobial peptides also caused the microorganisms to clump, suggesting a potential mechanistic connection (Spitzer et al., 2016). Another strain ($A\beta_{x\text{-}40}$) was a successful antifungal, but it did not produce an antibacterial effect, nor did it cause the bacteria to clump together. Spittzer et al. warned, however, that more research is necessary before this peptide can be discredited as an antibiotic since it may function indirectly by stimulating white blood cells.

Amyloid-β also appears to display antiviral activity. White et al. (2014) first demonstrated this activity by showing that amyloid-β significantly inhibited the ability of influenza A virus particles to infect human tracheobronchial epithelial cells. Bourgade et al. found similar results in 2015, when they tested amyloid-β against viral replication in human cell cultures. They discovered that amyloid-β effectively inhibited Herpes simplex virus 1 (HSV-1) replication, decreasing it by as much as 90% in some trials (Bourgade et al., 2015). Antiviral efficiency was related to the time that cells were exposed to amyloid-β relative to the virus—so that introducing amyloid-β before or during a viral infection was most effective—suggesting that the peptide functioned on free viral particles or interfered with their mechanisms for infecting cells (Bourgade et al., 2015). Interestingly, amyloid-β was ineffective against Human adenovirus type 5 (Had5), a non-enveloped virus, indicating that amyloid-β might target viral envelopes, which fuse with the target cell's plasma membrane to initiate infection (Bourgade et al., 2015).

The potential antiviral, antifungal, and antimicrobial properties of amyloid-β support the trade-off hypothesis. Furthermore, outside research projects—beyond the few studies that directly examine these properties—support the hypothesis by further indicating a role for amyloid-β in the immune system. For example, protein aggregates such as amyloid-β share important structural and functional similarities with antimicrobial peptides.

Functional and Structural Similarities of Amyloids with Antimicrobial Peptides

Antimicrobial peptides have been highly conserved throughout evolution and are present in many species. In fact, 2756 antimicrobial peptides from six kingdoms are recorded in the Antimicrobial Peptide Database. Depending on their structure, these peptides possess different mechanisms of attack and can target bacteria, viruses, or fungi. A subset of these proteins function by aggregating and causing bacteria to clump together—in a process called

agglutination—indicating a connection between amyloid-like aggregates and antimicrobial function. Torrent et al. (2012) characterized this interaction by tracking the aggregation of amyloid-like peptides on a bacterial cell membrane. Their evidence suggests that peptides aggregate on bacterial membranes, promoting bacterial cells to clump and disrupting their bilayers to both kill the bacteria and create a better target for phagocytic cells (Torrent et al., 2012). Furthermore, they proved the necessity of this process by comparing the effectiveness of an antimicrobial peptide known to form amyloid-like aggregates to that of a mutated peptide incapable of aggregating. The peptide's antimicrobial activity was decreased in the mutant (Torrent et al., 2012).

Bacterial agglutination and membrane disruption are important mechanisms of defense. Their connection to peptide aggregation is consistent with recent research on the function of amyloids. Kumar et al. (2016) found that soluble amyloid-β oligomers bind to microbial membranes, causing bacterial agglutination and inhibiting bacteria from adhering to host cells. Amyloid-β also appears to inhibit viruses by causing viral aggregation (White et al., 2014). A different amyloid polypeptide, secreted from the pancreas and called human islet polypeptide (hIAPP), appears to kill microbes by disrupting their membranes (Wang et al., 2012).

Similarities between the function of amyloids and other antimicrobial peptides are unsurprising, given their structural resemblances. Jang et al. (2008) found that the β-sheets associated with protegrin-1 (PG-1), an antimicrobial peptide that forms pores in bacterial membranes, possess a structure similar to the amyloid-β plaques involved in Alzheimer's pathology. The antimicrobial peptides that associate with microbial membranes often form amyloid-like fibrils. In fact, the amino acid sequences of antimicrobial and amyloid-like regions are highly similar: of all amino acids, 80% are found in (or absent from) these sequences in

corresponding amounts (Torrent et al., 2011). Thus, aggregation-prone regions within a protein are likely to generate antimicrobial activity.

Torrent et al. (2011) utilized this discovery to hypothesize that antimicrobial peptides were evolutionarily derived from amyloids. Their proposed explanation is consistent with our hypothesis that the antimicrobial properties of amyloid-β have contributed to its conservation throughout evolution. Amyloids may not have arisen as antimicrobial peptides, but developing that ability created new selection pressures on the trait. The close evolutionary history and entwined functions of amyloids and antimicrobial peptides underlies the fundamental trade-off between the neurological defects and the resistance to infection associated with these peptides.

Questioning the Framework of an Antagonistic Pleiotropy

With the proposed evolutionary framework, certain questions arise. Why is this trade-off expressed as an antagonistic pleiotropy? That is, why are symptoms only observed later in life? And is the positive selection pressure on antimicrobial amyloid peptides strong enough to sustain a trade-off? Measuring trade-offs is difficult, and in this situation, research on the pathological pathways of amyloid-β and its role in the innate immune system is still in progress. However, we can propose answers to these questions by utilizing existing research and basic principles in evolutionary medicine.

The incidence rate of Alzheimer's is highest among the elderly. Considering the trade-off between innate immunity and Alzheimer's, immunosenescence—the deterioration of the immune system with age—likely contributes to the age-related onset of this disease. Normal aging is associated with decreased immune function for multiple reasons: for example, chronic inflammatory processes may contribute to natural degeneration. The inflammatory response itself is associated with an antagonistic pleiotropy, as the mechanisms regulating the immune

system also contribute to the process of aging (Franceschi et al., 2000). Specifically, a pro-inflammatory state—a tendency towards systemic inflammation—is associated with old age. The problem is likely exasperated by selection pressures for pro-inflammatory genotypes, in place due to the importance fighting an infection at a young age (Vasto et al., 2007). Additionally, latent bacteria and viruses that lie dormant in the brain can be reactivated during the immunosuppression associated with aging (Itzhakia et al., 2016).

The age-dependence of Alzheimer's decreases negative selection pressures on the disease, increasing the likelihood for a trade-off. Evolution has tolerated Alzheimer's because of the weak selection against it and the positive selection on mechanisms of the immune system. Whether or not the antimicrobial properties of amyloid-β, in particular, confer a significant improvement to fitness has not been thoroughly examined. Thus, we cannot claim with certainty that this particular antagonistic pleiotropy contributes significantly to Alzheimer's; however, the evidence is suggestive. Studies demonstrate an association between survival and the presence of amyloid-β: in mice, for example, the knockout of the *bace1* gene—which produces a secretase that generates amyloid-β from APP—increased mortality rates (Dominguez et al., 2005). These associations have important implications for future clinical research and medical practices.

Clinical Implications and Future Research

If amyloid-β does participate in the innate immune response, therapies targeting peptide formation—such as therapies that target the secretases involved in cleaving APP— may have unintended consequences. These treatments may inhibit the body from launching a proper defense against infections. In a controlled trial, treatment with tarenflubril, a drug intended to lower amyloid-β by modulating the activity of γ-secretase, was associated with an increase in infections (Green et. al, 2009).

These potential negative consequences do not indicate that we should abandon research on amyloid-β, as it may still be an important target in treating Alzheimer's; however, potential effects to the immune system should be considered. The relationship in humans still requires a significant amount of research. For example, future studies should investigate whether there is an association between low amyloid-β levels and immunodeficiency.

The production of amyloid-β as an exaggerated cost of defense may also have implications for the development of new treatments. For example, preemptively addressing infections may reduce the prevalence of Alzheimer's by decreasing the stimulus for an innate immune response within the brain. With the devastating prospect of antibiotic resistance on the horizon, proposing to create policy changes based on infection prevention is not entirely feasible. However, simply recognizing the association between microbial infections and Alzheimer's prevalence is an important step for future research and policy.

Beyond treatments looking to address the apparent relationship between infections and Alzheimer's, other exciting research ideas are emerging. For example, Welling et al. (2015) recognized the role of pathogens in Alzheimer's pathogenesis and proposed a mechanism to use antimicrobial peptides as imaging biomarkers in studies of the disease. They noticed that future research on the role of pathogens in Alzheimer's would need improved mechanisms for detecting brain infections. Specifically, imaging biomarkers for CNS infections must be able to pass the blood-brain barrier—a trait that antimicrobial peptides possess. Thus, they proposed future research on the role of antimicrobial peptides, such as amyloid-β, both as actors in the CNS immune response and as imaging biomarkers (Welling et al., 2015).

Conclusion

As the leading cause of dementia, Alzheimer's disease negatively impacts the lives of millions of elderly citizens and their caretakers—and the number of patients is only projected to rise. Between 2016 and 2025, the number of people with Alzheimer's in each state in America is expected increase by at least fourteen percent (AA, 2016). Such a significant increase in the prevalence of disease will be both financially and emotionally taxing—thus, we must invest in the research that will best help alleviate the disease's causes and symptoms. Investigating the disease from diverse research perspectives will help to expand our understanding of its complexities. Specifically, by considering Alzheimer's disease from an evolutionary perspective, we gain important insights into the disease, unveiling why it exists in our population today, how we might develop new treatments, and what the limitations of current treatments are.

This discussion is particularly powerful in the context of innate immunity and the recent research on the antimicrobial properties of amyloid-β. If amyloid-β peptides are a critical component of the CNS innate immune response, they will have undergone notable selection pressure, and the consequence of their selection—Alzheimer's risk in later life—can be explained as an antagonistic pleiotropy and an exaggerated cost of defense. Evidence continues to emerge that supports this hypothesis, such as research that demonstrates a relationship between APP and survival, that connects inflammation to neurodegeneration, and that indicates an antimicrobial role for amyloids. This research indicates an intrinsic relationship between amyloid-β peptides and the CNS immune response and highlights the importance of considering the immunological consequences of Alzheimer's treatments—both those that are preexisting and those of the future.

References

Akiyama, H., S. Barger, S. Barnum, B. Bradt, J. Bauer, G. M. Cole, N. R. Cooper, *et al.* "Inflammation and Alzheimer's Disease." [In English]. *Neurobiology of Aging* 21, no. 3 (May-Jun 2000): 383-421.

Alzheimer's Association. "Alzheimer's Disease Facts and Figures." *Alzheimer's & Dementia* 12, no. 4 (2016): 459-509.

Bitting, L., A. Naidu, B. Cordell, and G. M. Murphy. "Beta-Amyloid Peptide Secretion by a Microglial Cell Line Is Induced by Beta-Amyloid-(25-35) and Lipopolysaccharide." [In English]. *Journal of Biological Chemistry* 271, no. 27 (Jul 1996): 16084-89.

Bloom, G. S. "Amyloid-Beta and Tau the Trigger and Bullet in Alzheimer Disease Pathogenesis." *Jama Neurology* 71, no. 4 (Apr 2014): 505-08.

Bourgade, Karine, Hugo Garneau, Genevieve Giroux, Aurelie Y. Le Page, Christian Bocti, Gilles Dupuis, Eric H. Frost, and Tamas Fueloep, Jr. "Beta-Amyloid Peptides Display Protective Activity against the Human Alzheimer's Disease-Associated Herpes Simplex Virus-1." *Biogerontology* 16, no. 1 (Feb 2015): 85-98.

Bourgade, Karine, Aurelie Le Page, Christian Bocti, Jacek M. Witkowski, Gilles Dupuis, Eric H. Frost, and Tamas Fueloep, Jr. "Protective Effect of Amyloid-Beta Peptides against Herpes Simplex Virus-1 Infection in a Neuronal Cell Culture Model." *Journal of Alzheimers Disease* 50, no. 4 (2016 2016): 1227-41.

Brier, M. R., B. Gordon, K. Friedrichsen, J. McCarthy, A. Stern, J. Christensen, C. Owen, *et al.* "Tau and a Beta Imaging, Csf Measures, and Cognition in Alzheimer's Disease." *Science Translational Medicine* 8, no. 338 (May 2016).

Bu, X. L., X. Q. Yao, S. S. Jiao, F. Zeng, Y. H. Liu, Y. Xiang, C. R. Liang, *et al.* "A Study on the Association between Infectious Burden and Alzheimer's Disease." [In English]. *European Journal of Neurology* 22, no. 12 (Dec 2015): 1519-25.

Bufill, E., R. Blesa, and J. Agusti. "Alzheimer's Disease: An Evolutionary Approach." *Journal of Anthropological Sciences* 91 (2013): 135-57.

Cassar, M., and D. Kretzschmar. "Analysis of Amyloid Precursor Protein Function in Drosophila Melanogaster." *Frontiers in Molecular Neuroscience* 9 (Jul 2016).

Cipriani, G., C. Dolciotti, L. Picchi, and U. Bonuccelli. "Alzheimer and His Disease: A Brief History." *Neurological Sciences* 32, no. 2 (Apr 2011): 275-79.

Coulson, E. J., K. Paliga, K. Beyreuther, and C. L. Masters. "What the Evolution of the Amyloid Protein Precursor Supergene Family Tells Us About Its Function." *Neurochemistry International* 36, no. 3 (Mar 2000): 175-84.

Demuro, A., I. Parker, and G. E. Stutzmann. "Calcium Signaling and Amyloid Toxicity in Alzheimer Disease." *Journal of Biological Chemistry* 285, no. 17 (Apr 2010): 12463-68.

Finch, C. E., and J. J. Marchalonis. "Evolutionary Perspectives on Amyloid and Inflammatory Features of Alzheimer Disease." *Neurobiology of Aging* 17, no. 5 (Sep-Oct 1996): 809-15.

Fowler, D. M., A. V. Koulov, W. E. Balch, and J. W. Kelly. "Functional Amyloid - from Bacteria to Humans." *Trends in Biochemical Sciences* 32, no. 5 (May 2007): 217-24.

Glass, D. J., and S. E. Arnold. "Some Evolutionary Perspectives on Alzheimer's Disease Pathogenesis and Pathology." *Alzheimers & Dementia* 8, no. 4 (Jul 2012): 343-51.

Haass, C., and D. J. Selkoe. "Soluble Protein Oligomers in Neurodegeneration: Lessons from the Alzheimer's Amyloid Beta-Peptide." *Nature Reviews Molecular Cell Biology* 8, no. 2 (Feb 2007): 101-12.

Hardy, J. "The Amyloid Hypothesis for Alzheimer's Disease: A Critical Reappraisal." *Journal of Neurochemistry* 110, no. 4 (Aug 2009): 1129-34.

Hardy, J., and D. J. Selkoe. "Medicine - the Amyloid Hypothesis of Alzheimer's Disease: Progress and Problems on the Road to Therapeutics." *Science* 297, no. 5580 (Jul 2002): 353-56.

Hardy, John A., and Gerald A Higgins. "Alzheimer's Disease: The Amyloid Cascade Hypothesis." *Science* 256, no. 5054 (1992): 184-85.

Heber, S., J. Herms, V. Gajic, J. Hainfellner, A. Aguzzi, T. Rulicke, H. Kretzschmar, *et al.* "Mice with Combined Gene Knock-Outs Reveal Essential and Partially Redundant Functions of Amyloid Precursor Protein Family Members." *Journal of Neuroscience* 20, no. 21 (Nov 2000): 7951-63.

Hoeijmakers, L., Y. Heinen, A. M. van Dam, P. J. Lucassen, and A. Korosi. "Microglial Priming and Alzheimer's Disease: A Possible Role for (Early) Immune Challenges and Epigenetics?" [In English]. *Frontiers in Human Neuroscience* 10 (Aug 2016): 15.

Hornsten, A., J. Lieberthal, S. Fadia, R. Malins, L. Ha, X. M. Xu, I. Daigle, *et al.* "Apl-1, a Caenorhabditis Elegans Protein Related to the Human Beta-Amyloid Precursor Is Essential for Viability." *Proceedings of the National Academy of Sciences of the United States of America* 104, no. 6 (Feb 2007): 1971-76.

Ishii, T., S. Haga, and F. Shimizu. "Identification of Components of Immunoglobulins in Senile Plaques by Means of Fluorescent-Antibody Technique." *Acta Neuropathologica* 32, no. 2 (1975): 157-62.

Itzhaki, R. F., R. Lathe, B. J. Balin, M. J. Ball, E. L. Bearer, H. Braak, M. J. Bullido, *et al.* "Microbes and Alzheimer's Disease." [In English]. *Journal of Alzheimers Disease* 51, no. 4 (2016): 979-84.

Jang, H., B. Ma, R. Lal, and R. Nussinov. "Models of Toxic Beta-Sheet Channels of Protegrin-1 Suggest a Common Subunit Organization Motif Shared with Toxic Alzheimer Beta-Amyloid Ion Channels." *Biophysical Journal* 95, no. 10 (Nov 2008): 4631-42.

Kumar, A., A. Singh, and Ekavali. "A Review on Alzheimer's Disease Pathophysiology and Its Management: An Update." *Pharmacological Reports* 67, no. 2 (Apr 2015): 195-203.

Kumar, D. K. V., S. H. Choi, K. J. Washicosky, W. A. Eimer, S. Tucker, J. Ghofrani, A. Lefkowitz, *et al.* "Amyloid-Beta Peptide Protects against Microbial Infection in Mouse and Worm Models of Alzheimer's Disease." [In English]. *Science Translational Medicine* 8, no. 340 (May 2016): 15.

Lee, H. G., X. W. Zhu, R. J. Castellani, A. Nunomura, G. Perry, and M. A. Smith. "Amyloid-Beta in Alzheimer Disease: The Null Versus the Alternate Hypotheses." *Journal of Pharmacology and Experimental Therapeutics* 321, no. 3 (Jun 2007): 823-29.

Lio, D., F. Licastro, L. Scola, M. Chiappelli, L. M. Grimaldi, A. Crivello, G. Colonna-Romano, *et al.* "Interfleukin-10 Promoter Polymorphism in Sporadic Alzheimer's Disease." *Genes and Immunity* 4, no. 3 (Apr 2003): 234-38.

Lynch, M. A. "The Impact of Neuroimmune Changes on Development of Amyloid Pathology; Relevance to Alzheimer's Disease." *Immunology* 141, no. 3 (Mar 2014): 292-301.

Mawanda, Francis, and Robert Wallace. "Can Infections Cause Alzheimer's Disease?" [In English]. *Epidemiologic reviews* 35 (2013 (Epub 2013 Jan 2013): 161-80.

McManus, R. M., S. C. Higgins, K. H. G. Mills, and M. A. Lynch. "Respiratory Infection Promotes T Cell Infiltration and Amyloid-Beta Deposition in App/Ps1 Mice." [In English]. *Neurobiology of Aging* 35, no. 1 (Jan 2014): 109-21.

Miklossy, J. "Emerging Roles of Pathogens in Alzheimer Disease." [In English]. *Expert Reviews in Molecular Medicine* 13 (Sep 2011): 34.

Miklossy, J., A. Kis, A. Radenovic, L. Miller, L. Forro, R. Martins, K. Reiss, *et al.* "Beta-Amyloid Deposition and Alzheimer's Type Changes Induced by Borrelia Spirochetes." *Neurobiology of Aging* 27, no. 2 (Feb 2006): 228-36.

Mossmann, D., F. N. Vogtle, A. A. Taskin, P. F. Teixeira, J. Ring, J. M. Burkhart, N. Burger, *et al.* "Amyloid-Beta Peptide Induces Mitochondrial Dysfunction by Inhibition of Preprotein Maturation." *Cell Metabolism* 20, no. 4 (Oct 2014): 662-69.

Olsen, I., and S. K. Singhrao. "Inflammasome Involvement in Alzheimer's Disease." [In English]. *Journal of Alzheimers Disease* 54, no. 1 (2016): 45-53.

Pham, C. L. L., A. H. Kwan, and M. Sunde. "Functional Amyloid: Widespread in Nature, Diverse in Purpose." In *Amyloids in Health and Disease*, edited by S. Perrett. Essays in Biochemistry, 207-19, 2014.

Pimplikar, S. W. "Reassessing the Amyloid Cascade Hypothesis of Alzheimer's Disease." *International Journal of Biochemistry & Cell Biology* 41, no. 6 (Jun 2009): 1261-68.

Puzzo, D., L. Privitera, E. Leznik, M. Fa, A. Staniszewski, A. Palmeri, and O. Arancio. "Picomolar Amyloid-Beta Positively Modulates Synaptic Plasticity and Memory in Hippocampus." *Journal of Neuroscience* 28, no. 53 (Dec 2008): 14537-45.

Sanchez de Groot, N., M. Torrent, A. Villar-Pique, B. Lang, S. Ventura, J. Gsponer, and M. M. Babu. "Evolutionary Selection for Protein Aggregation." *Biochemical Society Transactions* 40 (Oct 2012): 1032-37.

Selkoe, D. J., and J. Hardy. "The Amyloid Hypothesis of Alzheimer's Disease at 25years." *Embo Molecular Medicine* 8, no. 6 (Jun 2016): 595-608.

Shariati, S. A. M., and B. De Strooper. "Redundancy and Divergence in the Amyloid Precursor Protein Family." *Febs Letters* 587, no. 13 (Jun 2013): 2036-45.

Small, S. A., and K. Duff. "Linking a Beta and Tau in Late-Onset Alzheimer's Disease: A Dual Pathway Hypothesis." *Neuron* 60, no. 4 (Nov 2008): 534-42.

Soscia, S. J., J. E. Kirby, K. J. Washicosky, S. M. Tucker, M. Ingelsson, B. Hyman, M. A. Burton, *et al.* "The Alzheimer's Disease-Associated Amyloid Beta-Protein Is an Antimicrobial Peptide." [In English]. *Plos One* 5, no. 3 (Mar 2010): 10.

Spitzer, P., M. Condic, M. Herrmann, T. J. Oberstein, M. Scharin-Mehlmann, D. F. Gilbert, O. Friedrich, *et al.* "Amyloidogenic Amyloid-Beta-Peptide Variants Induce Microbial Agglutination and Exert Antimicrobial Activity." *Scientific Reports* 6 (Sep 2016).

Swerdlow, R. H. "Pathogenesis of Alzheimer's Disease." *Clinical Interventions in Aging* 2, no. 3 (2007): 347-59.

Tharp, W. G., and I. N. Sarkar. "Origins of Amyloid-Beta." *Bmc Genomics* 14 (Apr 2013).

Torrent, M., D. Pulido, M. V. Nogues, and E. Boix. "Exploring New Biological Functions of Amyloids: Bacteria Cell Agglutination Mediated by Host Protein Aggregation." [In English]. *Plos Pathogens* 8, no. 11 (Nov 2012): 8.

Torrent, M., J. Valle, M. V. Nogues, E. Boix, and D. Andreu. "The Generation of Antimicrobial Peptide Activity: A Trade-Off between Charge and Aggregation?". *Angewandte Chemie-International Edition* 50, no. 45 (2011): 10686-89.

Vasto, S., G. Candore, C. R. Balistreri, M. Caruso, G. Colonna-Romano, M. P. Grimaldi, F. Listi, *et al.* "Inflammatory Networks in Ageing, Age-Related Diseases and Longevity." [In English]. *Mechanisms of Ageing and Development* 128, no. 1 (Jan 2007): 83-91.

Wang, L., Q. Liu, J. C. Chen, Y. X. Cui, B. Zhou, Y. X. Chen, Y. F. Zhao, and Y. M. Li. "Antimicrobial Activity of Human Islet Amyloid Polypeptides: An Insight into Amyloid Peptides' Connection with Antimicrobial Peptides." [In English]. *Biological Chemistry* 393, no. 7 (Jul 2012): 641-46.

White, Mitchell R., Ruth Kandel, Shweta Tripathi, David Condon, Li Qi, Jeffrey Taubenberger, and Kevan L. Hartshorn. "Alzheimer's Associated Beta-Amyloid Protein Inhibits Influenza a Virus and Modulates Viral Interactions with Phagocytes." *Plos One* 9, no. 7 (Jul 2 2014).

Williams, G. C. "Pleiotropy, Natural-Selection, and the Evolution of Senescence." *Evolution* 11, no. 4 (1957): 398-411.

Williams, W. M., S. Torres, S. L. Siedlak, R. J. Castellani, G. Perry, M. A. Smith, and X. W. Zhu. "Antimicrobial Peptide Beta-Defensin-1 Expression Is Upregulated in Alzheimer's Brain." [In English]. *Journal of Neuroinflammation* 10 (Oct 2013): 11.

Yao, Z. X., and V. Papadopoulos. "Function of Beta-Amyloid in Cholesterol Transport: A Lead to Neurotoxicity." *Faseb Journal* 16, no. 10 (Aug 2002): 1677-+.

Zheng, C., X. W. Zhou, and J. Z. Wang. "The Dual Roles of Cytokines in Alzheimer's Disease: Update on Interleukins, Tnf-Alpha, Tgf-Beta and Ifn-Gamma." *Translational Neurodegeneration* 5 (Apr 2016).