Journal of Alzheimer's Disease 45 (2015) 349–362
DOI 10.3233/JAD-142841
IOS Press

Hypothesis

Mechanisms of Molecular Mimicry Involving the Microbiota in Neurodegeneration

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Accepted 17 December 2014

Abstract. The concept of molecular mimicry was established to explain commonalities of structure which developed in response to evolutionary pressures. Most examples of molecular mimicry in medicine have involved homologies of primary protein structure which cause disease. Molecular mimicry can be expanded beyond amino acid sequence to include microRNA and proteomic effects which are either pathogenic or salutogenic (beneficial) in regard to Parkinson's disease, Alzheimer's disease, and related disorders. Viruses of animal or plant origin may mimic nucleotide sequences of microRNAs and influence protein expression. Both Parkinson's and Alzheimer's diseases involve the formation of transmissible self-propagating prion-like proteins. However, the initiating factors responsible for creation of these misfolded nucleating factors are unknown. Amyloid patterns of protein folding are highly conserved through evolution and are widely distributed in the world. Similarities of tertiary protein structure may be involved in the creation of these prion-like agents through molecular mimicry. Cross-seeding of amyloid misfolding, altered proteostasis, and oxidative stress may be induced by amyloid proteins residing in bacteria in our microbiota in the gut and in the diet. Pathways of molecular mimicry induced processes induced by bacterial amyloid in neurodegeneration may involve TLR 2/1, CD14, and NFκB, among others. Furthermore, priming of the innate immune system by the microbiota may enhance the inflammatory response to cerebral amyloids (such as amyloid-β and α-synuclein). This paper describes the specific molecular pathways of these cross-seeding and neuroinflammatory processes. Evolutionary conservation of proteins provides the opportunity for conserved sequences and structures to influence neurological disease through molecular mimicry.

Keywords: Alzheimer's disease, amyloid, bacterial amyloid, metagenome, microbiota, neurodegenerative diseases, neuroinflammation, oxidative stress, Parkinson's disease

INTRODUCTION

The concept of mimicry was offered initially by Bates to describe similarity of structure in Lepidoptera developed as a result of evolutionary pressures [1]. Molecular mimicry (MM) was proposed by Damian who pointed out that natural selection has led parasites to mimic antigens of their hosts [2]. That is, the sharing of antigens between microbe and host may help the microbe avoid immune detection [2]. Evolutionarily conserved epitopes can clearly be involved in a pathogenic manner in MM, such as in autoimmune disorders, as well as in salutogenic (health-giving) mechanisms [3]. The protection against smallpox (variola) provided by exposure to vaccinia (derived from cowpox) is an example of this salutogenic influence [3]. In autoimmunity it is well recognized that similarity between host and foreign antigens can lead to humoral as well as cell mediated antibody responses targeting foreign antigens that cause disease through influences on host proteins. The nature of the structural homology in MM has usually been related to the primary structure of proteins (amino acid sequence). It has been proposed that MM may be

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ISSN 1387-2877/15/$35.00

responsible for ulcerative colitis because of similarity of primary structures between gut epithelial cells and bacteria. The foreign antigen eliciting MM has most often been reported to be present in bacteria or animal viruses. The concept of MM can be expanded to include the ability of foreign proteins from plant viruses to induce autoimmunity [4–6]. Plant proteins in food may also elicit MM and cause demyelination [7]. Furthermore, we have proposed that microRNA mechanisms may be involved in MM [8]. Finally, I propose that bacterial proteins may elicit cross-seeded misfolding, inflammation and oxidative stress, and cellular toxicity in the neurodegenerative conformational disorders, initiating or otherwise influencing the development of Parkinson's disease (PD), Alzheimer's disease (AD), and related conditions.

MM may develop when there is an evolutionary desirable advantage to the similarity (as described by Bates) [1]. The chance similarity of protein structures, as is the case for rheumatic heart disease, may also result in MM-induced processes [9]. The concepts and mechanisms of MM have recently been delineated by Oldstone, who notes that only 5-6 amino acids are needed for generation of a monoclonal antibody response [10]. Proteins that share amino acid sequences or conformation may elicit MM as long as they are not identical (if they are identical they will not be recognized as foreign and there will be immune tolerance) [10]. Therefore, the opportunity arises for evolutionarily conserved proteins, as well as proteins that contain homologies entirely by chance, to be involved in MM. These homologies creating the opportunity for MM may involve primary, secondary, or tertiary protein structures or the nucleotide sequence of RNA in animal or plant viruses, bacteria, or food (See Table 1). Examples of ways in which these mechanisms of MM may influence the nervous system will now be reviewed.

Table 1
Molecular mimicry may develop in response to similarities in structure at these levels

Level	Example	REF
Primary protein structure	Rheumatic fever	[9]
Nucleotide sequence	MicroRNAs	[8]
Tertiary protein structure	Cross-seeding of protein misfolding	[64, 65]

MOLECULAR MIMICRY INVOLVING PRIMARY PROTEIN STRUCTURE

Potato virus Y and AD

Following the discovery that immunization with amyloid-β (Aβ) protein causes improvement in the biological and pathological feature of Aβ deposition in transgenic animals by Schenk and colleagues in 1999, a wide range of animal and human studies have been devoted to the immunological features of AD [11]. It is clear that immune responses targeting the Aβ protein have a profound biological effect on Aβ deposition in animals and humans [11]. However, it is not yet known whether this effect can be developed for therapeutic use. This work led to the suggestion that antibodies targeting the Aβ protein in healthy people may be protective [4]. Studies of anti-Aβ antibodies in AD and healthy controls have shown that levels may be increased, decreased, or unchanged [4, 12]. These studies need to account for the influence of circulating Aβ antibody levels on antibody assays [12]. Protective catalytic IgM antibodies efficiently cleaving the Aβ protein have also been reported [13]. Despite conflicting studies, it has been demonstrated that many people produce antibodies targeting Aβ. The factors responsible for development of anti-Aβ antibodies and their role in AD remain unclear.

For these reasons, we performed a BLAST search (Basic Local Alignment Search Tool, NCBI, National Library of Medicine, US) and found that significant homology exists between the human Aβ protein and the nuclear inclusion B protein of potato virus Y [4]. We observed that mice inoculated with potato leaf infected with potato virus Y develop antibodies that bind to human and animal Aβ [4]. The question remains if exposure to potato virus Y may elicit antibodies that bind to Aβ and enhance clearance from the brain, lowering the risk of AD.

Plant viruses are widespread in the environment and have major economic impact on agriculture. Live pepper viruses are found in sauces made from Tabasco peppers (*Capsicum frutescens*). Although plant viruses are not believed to replicate in any animal host, it has been demonstrated that they survive inactivation in the gut, are taken up through the intestinal barrier, and circulate through the body with a wide distribution [14]. The pepper mild mottle virus is highly abundant in human stool and can be acquired through oral intake. It is of interest that plant viruses evolved in part because of their capacity to tolerate survival in animal hosts, as they are transmitted through insect vectors. These interactions may be pathogenic if the induced antibodies developed in response to exposure to a plant virus cause disease, or salutogenic if the antibodies are protective, as in the proposed case of potato virus Y in AD

[4]. The possibility that antibodies to plant viruses are involved in human diseases has not been previously considered.

Tobacco mosaic virus (TMV) and PD

Many studies have shown that exposure to tobacco products as well as to solanaceous plants in the diet are protective against the development of PD [5, 6]. Although there are many theories to explain these effects the mechanisms are unclear. TMV is known to infect over 175 species of plants, especially those of the *Solanaceae* family and is the best studied plant virus. We found that all of 60 healthy controls have anti-TMV antibodies, mostly IgG, with higher titers in smokers than nonsmokers [5]. An intriguing homology of 6 identical amino acids was found between the TMV primary structure (36–41) and the sequence of the important mitochondrial membrane protein translocase of the outer mitochondrial membrane (TOMM 40L) (60–65), and mitochondrial dysfunction has been well documented in PD [5]. Further studies of anti-TMV antibodies are needed.

Aquaporins in brain and plants

The demyelinating disease neuromyelitis optica (NMO) is associated with antibodies to the astroglial water channel protein aquaporin 4 (AQP4). Water channels are clearly important for life in both plant and animals and aquaporins are highly conserved in animals and plants. We compared human AQP4 to plant and bacterial proteins to see if homologous structures preserved through evolution may be found that could explain the source of autoimmunity in NMO. We found that a sequence of plant aquaporin (maize ZmTIP4-1, 196–221) has high similarity to a known loop E epitope of human anti-AQP4 IgG antibodies from NMO patients (AQP4 207–232) (20 out of 26 amino acids identical) [7]. Sera from NMO patients showed reactivity to plant peptides as well as to plant tissue [7]. The opportunities for human autoimmune disease to be initiated through MM by exposure to plant aquaporins have not been considered.

MOLECULAR MIMICRY INVOLVING MICRORNA MECHANISMS

A further consideration regarding primary sequence homology concerns the consideration that plant viruses may be processed in the body through mechanisms involving microRNAs. RNAs are "the most functionally diverse biological macromolecule" and have complex three-dimensional structures [15]. MicroRNAs are small 18–22 nucleotide long non-coding molecules that regulate protein synthesis. It is estimated that microRNA pathways are involved in the regulation of gene expression for at least a third of all human brain proteins [16]. Humans are exposed to many plant viruses which contain RNAs, establishing the potential for MM to impact health (see Table 2). As noted above, plant viruses are taken up through the gut and well distributed. We considered the possibility that homology of nucleotide sequence in plant viral RNA could lead to the production of microRNAs, which influence protein expression in animal hosts. This process has been already demonstrated with animal viruses: RNA from herpes virus saimiri binds to and initiates the degradation of human MIR-27, resulting in enhanced infection [17, 18]. We found that several plant viruses contain nucleotide sequences which are significantly homologous to human microRNA sequences [8]. In several cases, the plant viruses contain nucleotide sequences which exactly match the seed sequence of human microRNAs, in either parallel or anti-parallel directions [8]. Plant viral RNA may also interact with RNA binding proteins with influences on protein expression. There is also the opportunity for the RNA of plant viruses to mimic long non-coding RNAs and other RNA species. Furthermore, the influence of microRNAs from plants consumed in the diet on lipid metabolism has been demonstrated in mammals [19]. The consequences of these cross-kingdom sequence similarities need to be further explored.

Table 2

Agents inducing molecular mimicry	REF
Bacteria*	[9, 44, 56]
Animal viruses*	[3]
Plant viruses*	[4, 5, 15]
Amyloids proteins in food	[50, 56]
Bacteria that make amyloid proteins**	
Bacillus subtilis	
Escherichia coli	
Klebsiella pneumoniae	
Mycobacterium tuberculosis	
Salmonella enterica	
Salmonella typhimurium	
Staphlococcus aureus	
Streptococcus mutans, coelicolor	
Xanthomonas axonopodis	

*Exogenous as well as endogenous (found in the microbiota). **The list is incomplete. Genes for producing amyloids are also found in these phylum of bacteria: *Actinobacteria, Bacteroidetes, Chloroflexi, Firmicutes, Proteoabacter, Thermodesulfobacteria* [46, 47, 49, 64].

MOLECULAR MIMICRY INVOLVING TERTIARY STRUCTURE

Proteomics

The neurodegenerative disorders PD, AD, amyotrophic lateral sclerosis, frontotemporal lobar degeneration, Lewy body dementia, and progressive supranuclear palsy are all of sporadic origin in 90–99% of cases and are all associated with amyloid misfolding of neuronal proteins in the central nervous system. In the sporadic forms of each disorder, the factors responsible for the initiation of protein misfolding are unknown. Recently it has been shown that the disease associated proteins α-synuclein (AS), found in PD, and Aβ, found in AD, as well as tau, are capable of transmission of misfolding from one brain region to another and from an animal or human to a susceptible host [20, 21] (for review, see [22, 23]). Amyloid misfolding involving oligomeric species, a hallmark of these neurodegenerative diseases, is believed to be a main cause of neuronal death. I propose that the misfolding of the neuronal proteins found in PD, AD, and related disorders is triggered by MM induced templated cross-seeding, similar to the mechanism proposed for misfolding in the prion diseases.

PD is characterized by accumulation of aggregated and phosphorylated AS in Lewy bodies and Lewy neurites [24–26]. Aggregated AS is a form of amyloid found in many brain regions as well as in neurons in the myenteric plexus of the gut wall in PD patients, and in aged rats [24, 25]. AS, as well as Aβ, tau, FUS, and TDP43 can induce autocatalytic protein misfolding following a rate limiting nucleation event, which spreads within the central nervous system to cause disease [23, 27, 28]. The mechanism of this self-templated nucleation dependent spreading of amyloid misfolding is analogous to that of the prion disorders, such as Creutzfeldt Jakob disease (CJD), bovine spongiform encephalopathy, and others [23, 28]. The spreading in the brain of misfolded AS and tau appears to be along neuronal connections through axonal membranes utilizing a prion-like cell-to-cell spread with neuronal connectivity, not proximity, being critical [29–31]. This work has led to the proposal that the amyloid proteins of the neurodegenerative disorders are prions [32]. Nonetheless, the source or origin of the misfolding in PD or AD is currently unknown. Prusiner has suggested that the initial event is the stochastic (random) misfolding of the prion-like protein [32]. This may not be the only mechanism of this critical misfolding. We must ask: can the misfolding be induced by endogenous or exogenous factors, and what is the initial trigger?

In the case of bovine spongiform encephalopathy-induced new variant CJD, the origin of the misfolding is known to come from ingested bovine spongiform encephalopathy prions, which cause prion transformation initially in gut neurons. The first brain region found to contain the scrapie prion in sheep is reported to be the dorsal motor nucleus of the vagus nerve in the medulla [33]. The dorsal motor nucleus of the vagus contains the neuronal cell bodies of the vagus nerve fibers which innervate the gut. Most remarkably, this is also one of the first brain regions to contain misfolded AS in PD [24, 25, 34]. Furthermore, myenteric neurons in the gut wall contain AS deposits in PD. These findings suggest that the origin of protein misfolding in PD may reside in the gut.

Another site of initiation of protein misfolding may be the olfactory epithelium. Olfactory impairment and anosmia have been associated with aging in humans as well as with several neurodegenerative disorders including PD, AD, and others. The molecular mechanisms underlying olfactory decline in these disorders remain unclear. There is early involvement of the olfactory system in PD and AD and the olfactory cortex is structurally linked to the site of main PD pathology, the substantia nigra [35, 36]. Olfactory pathology has been reported to predict Braak staging in AD [37]. Prion seeding of the nose has also been recently found in CJD [38]. It is important to note that there is a close spatial relationship between the olfactory receptors (which are processes of neurons from the brain) and bacteria present in the nose.

If the protein misfolding problem in PD and AD originates in the gut and/or nose, which inducing factors may be responsible? There has been a great expansion of interest and knowledge about the microbial metagenome. The recent human microbiome project has brought renewed attention to the resident bacterial population of the human body (Human Microbiome Project Consortium) [39]. The human microbiome refers to the collective DNA sequences of all the organisms residing on or in a person. It is estimated that there are 10X more cells and 130X more DNA in the metagenome than in our own bodies [40, 41]. The volume of gut bacteria is estimated at 250 ml in adults, with $\sim 10^{11}$ cells per ml of colonic contents [42]. The collective organisms in the gut (which includes the nose, oropharynx, esophagus, stomach, and intestines) whose DNA contributes to the metagenome is referred to as the microbiota. These organisms residing on the skin, in the mouth

and gut and other regions have been shown to be involved in diabetes mellitus, hypertension, atherosclerosis, coronary heart disease, ankylosing spondylitis, liver disorders, and other conditions [43, 44]. Although our evolution has occurred simultaneously with the evolution of our microbiota, the role of these organisms on brain health has not been addressed.

Changes in the microbiota have been demonstrated in aging, with reduced diversity of organisms linked to residential community, reduced dietary diversity, frailty, and other health outcomes [45]. Other influences on the microbiota in the aged include medications, impaired gastrointestinal motility, impaired gut-blood barrier, and decreased immune function. Declining production of chaperones necessary for proper protein folding may also be involved. These age-related changes in the gut microbiota may all be linked to the age-relatedness of the neurodegenerations.

Bacteria found in the human microbiota have been shown to produce extracellular amyloid proteins [46–48]. Bacterial amyloid proteins are adaptive and enhance adhesion, aggregation, biofilm formation, tissue invasion, colonization, and infectivity [46]. The formation of amyloid by proteins has been considered for decades to be an entirely pathological event. However, recently it has been shown that functional amyloids are found in yeast, bacteria, rodents, and humans [47, 49]. The ability to form amyloid folds appears to be a highly conserved pathway with adaptive value for information transfer and structural dynamics [49]. The prion forming ability of proteins in yeast and fungi is believed to be as much as 1 billion years old [50]. It has been proposed that prion formation in the brain is involved in memory storage [51]. The extracellular amyloid protein called curli produced by *E. coli* and *S. typhimurium* enhances colonization and biofilm development [46, 52]. Curli fibers bind Congo red and host proteins and have well-developed mechanisms of regulated expression [46]. Curli fibers have been shown to mediate internalization into host cells and contain short peptide repeats similar to those of yeast and animal prions [53]. While bacterial amyloids are now well documented, there have been no investigations of their role in brain disease [54]. I propose two mechanisms by which amyloid from bacteria may induce or influence human neurodegeneration: 1) protein misfolding and 2) induction of neuroinflammation and oxidative stress (see Table 3).

Despite the considerable evidence that many of the bacterial species residing in the body make amyloid proteins there has been little work on the presence of bacterial amyloid in the gut. (See Table 2) [52, 55]. The bacterial protein curli from *E. coli* has been found in the gastrointestinal tract of humans [52]. *Streptococcus mutans* is a widespread oral symbiont which makes an amyloid protein and has been linked to hemorrhagic stroke [48, 55]. Also, the ability of amyloid in the gut to induce protein misfolding and systemic disease has been demonstrated in systemic amyloidosis (see "Amyloidogenic potential of foie gras" [56]). Xing et al. showed that orally delivered seeds composed of homologous peptide caused amyloid deposits in a mouse model of apolipoprotein A-ll amyloidosis [57]. Proteins from gut bacteria may gain access to neurons in the myenteric plexus because of the sampling of gut contents by epithelial microfold (M) cells as well as dendritic cells which deliver antigens to immune cells in Peyer's patches [58, 59]. It has also been shown that prions are taken up by follicle-associated epithelial cells in the gut, and then delivered by macrophages and dendritic cells to enteric nerves [60]. The only barrier in the nose for entry of molecules into the brain is the plasma membrane of olfactory neurons, which are exposed to air in the roof of the nose. Little et al. observed that intranasal inoculation of *Chlamydia pneumonia* in BALB/c nontransgenic mice caused amyloid deposits in the brain and an elevated inflammatory response [61]. Furthermore, it has been shown that olfactory ensheathing cells recognize and endocytose bacteria [62, 63]. The relationships between exposure to bacterial amyloids to misfolding of AS, Aβ, and other proteins related to neurodegeneration have not been investigated.

How might bacterial amyloid proteins influence neurodegenerative processes? The transmission of misfolding from one molecule of a protein to another molecule of the same protein was proposed originally by Prusiner as the mechanism for the prion disorders

Table 3

Proposed mechanisms of MM in ND	Molecular Pathways	REF
Induction of protective anti-Aβ antibodies	epitope homology	[4]
Cross-seeding of protein misfolding	prion transmission	[22, 23, 28, 64]
Neuroinflammation and oxidative stress	TLR2/1, CD14, NFκB, iNOS	[79, 83, 88]

MM, molecular mimicry; ND, neurodegeneration; Aβ, amyloid-β.

(as shown by the conversion of PrP^{c} to PrP^{sc}) [32]. It has also been shown that one misfolded molecule may elicit the misfolding of a different molecule (cross-seeding: an endogenous or exogenous protein may induce beta sheet misfolding of a host protein with a different primary structure). A wide range of environmental amyloid fibrils has been shown to cause cross-seeding of Aβ aggregation *in vitro* [64, 65]. Lee's group has shown that AS aggregates seed aggregation of tau [22]. Morales and associates have shown that prion inoculations in AD model transgenic mice cause the acceleration of both disorders [65]. I propose that cross-seeding of the neurodegenerative disorder proteins may be induced by environmental amyloids such as those produced by bacteria. The seed may initiate changes in proteostasis (misfolding) or accelerate the important lag phase of nucleation.

What aspects of cross–seeding may explain the complex phenotypic heterogeneity of the neurodegenerative disorders? Strains have been well recognized in prions as responsible for the unique characteristics of potency, incubation time, host specificity, and disease phenotype [32]. The 3D physical nature of the amyloid fold, which is stable and propagated *in vivo*, is thought to be responsible for these features of a prion strain. It has been established that a single infectious prion protein can become misfolded into several different conformations, resulting in strains [66]. Recently it has been reported that the disease-associated amyloids AS and Aβ also show the features of strains with unique fibril structures which determine the structure of associated pathologies [22, 67, 68]. Hartman et al. have documented the ability of bacterial amyloids to induce cross-seeding, including interactions with proteins of dissimilar sequences [64]. The unique structures of prion strains may be predetermined by the structure of the bacterial (or other) amyloid which induced the initial cross-seeding misfolding event.

Furthermore, the possibility that bacterial amyloids may induce cross-seeding of endogenous proteins such as Aβ, AS, tau, and others is supported by the observation that the bacterial amyloid protein curli is recognized by the conformation specific anti-Aβ oligomer antibody A11, as reported by Glabe and colleagues [69, 70]. This work suggests that there are soluble oligomers that have a common generic structure. Amyloids have also been found in dietary items, including milk, meat, maize, berries, fungi, and organ products, as well as various other plants [71, 72]. Villar-Pique has suggested that the production of amyloid conformations in genetically-modified plants deserves investigation [73].

NEUROINFLAMMATION AND OXIDATIVE TOXICITY

The large surface area of the oral/nasal cavities and gut epithelial layer is the dominant interface for interactions between bacteria and our own cells. It is necessary for the maintenance of homeostasis that the immune system be aware of the gut bacterial contents [74]. The gut is the largest immune organ in the body and the huge antigenic load contained within would be of great potential danger if it was not subject to continuous surveillance [74]. It has been recently demonstrated that the microbiota have a strong influence on the immune system. The production of anti-inflammatory Treg cells may be enhanced by addition of "rationally selected" Clostridia strains [75]. Furthermore it has been proposed that the immune system undergoes "peripheral education" by the intestinal organisms, as germ-free mice have deficient immunity [76]. Surveillance of gut antigens is enhanced by the ability of immune cells (monocytes, macrophages, dendritic cells, and some epithelial cells) to readily recognize pathogen associated molecular patterns (PAMPS) [77]. Bacterial amyloid is recognized as a PAMP and causes activation of toll-like receptor-2 (TLR2) and other important mediators of inflammation including NFκB, a master-regulatory molecule of inflammation, as well as TLR1 and CD14 [78, 79]. TLRs are expressed on immune cells as well as neurons and influence the production of a wide array of inflammatory molecules including cytokines and chemokines [80]. A wide array of molecules activate TLR2, including peptidoglycan and lipoteichoic acid as well as bacterial amyloid, AS, and Aβ [77].

Large numbers of T cells are found in the gut wall. These cells circulate widely and may enter the brain [81]. The gut is extensively innervated, including fibers supplying the smooth muscle, epithelium, blood vessels, and Peyer's patches. Immune molecules in the blood may reach the brain (either directly or indirectly) through several mechanisms: active transport across the blood-brain barrier, signaling in the intestinal lumen and propagation of secondary factors into the brain; spread to brain through the circumventricular organs, or signaling via nerves, such as the vagus [80–82]. The idea that inflammation in the brain may be linked to bacterial amyloid has been proposed by Trudler et al., who suggested that cerebral amyloid may mimic viral or bacterial infection resulting in glial cell activation through TLRs [83]. TLR2 activation has also been reported to cause Notch1 upregulation, which may enhance processes leading to AD [84].

Beginning with the pioneering work of McGeer and colleagues, it has been established that there is sterile inflammation in the brain in the neurodegenerative disorders [85, 86]. Neuroinflammation has been documented in PD, with a specific upregulation of TLR2 signaling and activation of microglia [87]. Richard et al. reported that TLR2 assists in clearance of Aβ from the brain in transgenic mice [88]. Increased expression of TLR2 (as well as TLR4) has also been found in peripheral blood mononuclear cells in AD [19, 82]. TLR signaling has also been found to involve microglial cells in the central nervous system, especially TLR2 [83]. Furthermore, TLR2 has been shown to be important for the regulation of intestinal barrier integrity. Activation of innate immunity can also influence goblet cell mucus secretion and thereby the gut-blood barrier [89]. Another important molecule of the innate immune system response is CD14, which is involved in the activation of the TLR2/TLR1 complex in response to lipopolysaccharides or bacterial amyloid, as well as the immune reaction to pathogens [90, 91]. Peripheral inflammatory processes have been shown to influence several forms of neurodegeneration [80, 92]. Bodea and colleagues reported that peripherally-induced inflammation activates the microglial complement pathway to damage dopaminergic neurons in mice [93].

TLR2/1 activation and CD14 expression may lead to upregulation of NFκB expression and induction of nitric oxide synthase, with resultant inflammation and oxidative toxicity [79]. Oxidative toxicity with production of free oxygen and nitrogen radicals has been implicated in all neurodegenerative disorders [94]. It has been proposed by Perry, Smith, and colleagues that oxidative toxicity is a primary process in AD with Aβ deposition occurring as a response to free radical production [95].

The potential role of the microbiota in autoimmunity is well illustrated by ankylosing spondylitis, which is associated with HLA B27 and *Klebsiella pneumonia* [10]. It has been reported that there is a 6 amino acid homology between HLA B27 and *Klebsiella pneumoniae* in regions exposed to the cell surface [10]. It has been proposed that ankylosing spondylitis occurs because of this MM, in which cross-reactive antibodies targeting *Klebsiella pneumoniae* residing in the colon attack self-antigens and cause inflammation in joints in persons with the HLA B27 genotype [96].

The important role of inflammation in neurodegeneration is also supported by the recent finding of rare genetic risk factors for AD, FTD, and PD that influence innate immunity: TREM2 (Triggering Receptor Expressed on Myeloid cells 2) and clusterin [97, 98]. TREM2 is widely expressed on circulating cells, microglia, and plaque associate myeloid cells. TREM2 stimulates phagocytosis, suppresses cytokine production and inflammation, and inhibits TLR signaling in peripheral macrophages and dendritic cells. Another component of the innate immune system is clusterin, which has also been found to be genetically linked to AD. Clusterin is expressed in M cells and the dendritic cells in Peyer's patches in the human gut [99].

I propose that inflammation as well as oxidative toxicity in PD and AD may be enhanced by exposure to bacterial amyloids as both bacterial amyloids, and the amyloid proteins Aβ and AS are recognized as PAMPs through a TLR 2 mediated pathway, leading to inflammation and oxidative toxicity. Immune cells primed by exposure to bacterial amyloid may be more responsive to the presence of Aβ or AS in the brain. These immune cells include both brain resident microglia as well as circulating macrophages that have access to the brain [81]. Immune activation produced by the microbiota may also delay elimination of important brain proteins such as Aβ, which are cleared by perivascular drainage pathways [100, 101].

Several groups have found that many older persons with Aβ deposits do not have dementia [102]. Akiyama and colleagues have observed that nondemented persons who have Aβ deposits demonstrate less inflammation than the Aβ deposits of persons with dementia [86]. Priming of microglia (as described by Perry, Holmes, and colleagues) and enhancement of related immune responses to Aβ, AS, and other misfolded proteins produced by bacterial amyloid may thus enhance dementia development [92, 103].

The role that inflammation plays in neurodegeneration is not well understood. It is curious to consider that the mechanisms proposed here may work in varying directions. Inflammation in the neurodegenerative disorders is limited to microgial/astroglial activation, complement, cytokine expression, and associated oxidative stress. The reason why there is not lymphocyte or macrophage accumulation is not clear (for review, see [104]). Immune responses to bacterial amyloid may be pathogenic if they lead to oxidative stress and damaging cytokines. Immune responses to bacterial amyloids may be protective if they enhance clearance of toxic oligomers. A beneficial response to inflammation in a mouse model of AD has been reported [105]. It has been observed that complement C3 deficiency reduces microglial priming and enhances plaque deposition, suggesting that the

complement mediated component of the immune response is beneficial [106]. Also, a beneficial effect of Aβ reactive T cells in mice has been observed [107] and Th2 based immune responses have been shown to be salutogenic in AD model mice [108].

Amyloids of exogenous origin may occupy chaperones, influencing the opportunity for misfolding to occur. It is also worth considering the observation that inhibition of fibrillization may lead to greater seeding potential and more toxic Aβ oligomers [109, 110]. Influences of the microbiota on clearance of misfolded proteins should also be considered.

It appears oversimplified to consider the potential role of proteomic or immune interactions in these disorders to be either entirely pathogenic or protective.

GENETIC AND EPIDEMIOLOGICAL CONSIDERATIONS

Interactions of genes and environment are, of course, critical factors in genesis of all diseases. The influence of the microbiota on health is certainly influenced by genes, although this matter has not been well studied. The interaction of environmental factors, human genes, and the gut is illustrated by variant CJD. Cases of CJD identified so far exclusively have the methionine homozygous (MM) genotype at codon 129 of the PRNP gene, and people who are heterozygotes (MV) or valine homozygotes (VV), are resistant [32]. Apolipoprotein E (ApoE) is the most important genetic risk factor for AD. The $\varepsilon 4$ allele of ApoE has been shown recently to also increase the risk for dementia in synucleinopathies, including PD [111]. Although several mechanisms for these effects have been proposed, it is not clear which are responsible. ApoE, as a lipid-handling gene, influences bile acid secretion in humans and mucin secretion in murine lung, and has immunomodulatory effects [112–115]. Bile is known to influence bacterial growth in the gut and the gut barrier is comprised, in part, by layers of mucin. The relationship between ApoE genotype, gut bacteria, and the gut-blood barrier has not been addressed. The consideration that ApoE genotype may influence the microbiota to favor the development of organisms triggering misfolding should be investigated. Also, the micobiota is known to modulate the lipidome, and may influence production of plasma phospholipids (such as phosphatidylinositol and glycoursodeoxycholic acid) reported to be higher in AD sera [116].

It has been observed that AD is less common in sub-Saharan Africa and India than in Western countries, even when correcting for the effects of survival [117]. The reasons for this lower prevalence and incidence are not clear, and have been attributed to the higher level of lifetime physical activity, lower levels of fat consumption, and higher levels of fruit, vegetable, and fiber intake in developing countries. The possibility that dietary influences on microbiota consumption are responsible for these effects deserves consideration. In particular, dietary fiber enhances the growth of colonic bacteria that produce short chain fatty acids which have systemic anti-inflammatory effects [118], which may be protective against several disease processes. Furthermore, potatoes in developing countries are more likely than those in Western countries to be infected with potato virus Y, as industrial agriculture has developed the use of sterile seed potatoes. The influence of exposure to potato virus Y (or other plant viruses) on health has not been well explored.

DISCUSSION

This paper has reviewed ways in which human health may be influenced by conserved protein and nucleotide sequences and protein folding patterns. The view presented here describes how the interaction of humans with our external and internal microbial ecosystems may be determinants of neuronal health and disease.

Investigations of the mechanisms suggested here may have implications for the multiple neurodegenerative proteinopathies, as these disorders involve similar scenarios of transmissible protein misfolding, neuroinflammation, and oxidative stress of unclear origin (AD, PD, frontotemporal lobar degeneration, amyotrophic lateral sclerosis, Lewy body dementia, CJD, cortical basal ganglionic degeneration, multiple system atrophy, progressive supranuclear palsy). Microglial activation through TLRs may be linked as well to CJD, HIV/AIDS, stroke, and multiple sclerosis. Inflammatory mechanisms and TLR2 are also involved in atherosclerosis [119]. Cerebrovascular changes have long been associated with AD, including enhancement of cognitive changes, white matter lesions, cerebral amyloid angiopathy, and microbleeds. Microbiota in the naso-oropharynx may impact vascular inflammation and oxidative stress to influence these processes [55, 120]. Nakano et al. have demonstrated the influence of oral bacteria on hemorrhagic stroke in humans [55].

An additional mechanism by which endogenous amyloids may influence health has been recently

Table 4
Locations where microbiota-host interactions may influence health*

Body site	Site of influence
Roof of nose	olfactory epithelium
Naso-oro-pharynx	vessels passing through and near sinuses going to brain
Mouth	olfactory epithelium, proximate brain vessels
Gut (stomach, small and large intestines)	myenteric neurons, autonomic nervous system, spinal cord and brain

*Microbiota may also influence health through circulating pathways.

demonstrated. Amyloids in human semen enhance infectivity of HIV and CMV [121, 122]. Several authors have proposed an important role for viral infection in late-life brain disorders. The influence of amyloids in the microbiota on viral diseases has not been considered.

SUMMARY

The neurodegenerative disorders all involve altered proteostasis and in most cases the agent initiating the misfolding is not known. The prominent pathology in enteric and olfactory neurons in PD suggests that the agent may be coming from the gut, including the oral/nasal/pharyngeal cavities. The opportunity for chronic exposure to foreign antigens in these regions is great. Functional amyloids are made by gut bacteria and may be the source of: 1) misfolding of neuronal proteins through cross-seeding and 2) activation of the innate immune system and priming of neuroinflammation. The unique structure of the foreign amyloid may induce specific misfolding patterns (strains) which may be responsible for the variety of phenotypes of the neurodegenerative disorders.

Similarities of nucleotide sequence and protein configuration that involve primary, secondary, or tertiary structure may influence health and disease involving immunological, miRNA, or proteomic mechanisms. Salutogenic processes may be enhanced through MM which may inhibit myriad disease processes. It is important to consider the extensive conservation of protein sequences and structures through evolution and the opportunities for human health to be affected by our interactions with plants, plant and animal viruses, prokaryotes, and other forms of life. The opportunities for cross-kingdom interactions (bacteria, plants, animals, and others) must be considered. The microbiota is a rich source of these interactions and the possibility of MM originating in the gut including the oral/nasal cavities is just beginning to be explored. Proteins with amyloid configurations are widespread in the environment because of their adaptive value [46, 53]. The possibility that bacterial or other nonhuman amyloid proteins themselves can function as prions in mammalian hosts deserves consideration.

More specifically, I propose that amyloid cross-seeding in neurons is triggered by amyloid-containing bacteria in the nose and/or gut. The trigger for AS misfolding in PD may be from bacterial amyloids that influence the brain through the vagus and other nerves from the gut and/or directly through the roof of the nose to the olfactory cortex. The trigger for Aβ misfolding may also originate in the nose or gut (See Table 4). At the same time, bacterial and other exogenous amyloids may induce inflammation and oxidative stress through TLR-mediated pathways leading to enhanced immune responses to endogenous amyloids such as AS or Aβ.

It would be desirable if the potential for cross-seeding between two candidate proteins could be predicted through computer modeling. Unfortunately, our understanding of protein structure and the mechanisms of cross-seeding are not currently sufficient to make *in silico* prediction possible. Similarly, exploring opportunities for MM by searching for homologous sequences is no longer adequate: secondary and tertiary structures need to be considered as well. Investigation of the mechanisms proposed above is limited by the lack of knowledge of which bacterial amyloid proteins may be involved. Preliminary studies are underway to assess the role of the microbiota on protein folding and inflammation in animals and humans.

The concepts discussed here have significant translational potential. Therapeutic options include antibiotics to remove harmful bacteria, prebiotics to enhance the growth of desired organisms, and probiotics to provide desired bacteria. Diet is clearly important as well. In particular, the importance of diversity of diet leading to diversity of the microbiota is a new concept, which is clinically important [45, 123]. Therapies to alter the amyloids produced by bacteria, or decrease their production, may also be developed [124]. It may also be possible to work on modifying the response of the immune system to the microbiota.

NOTE ADDED IN PROOF

An additional route by which luminal proteins can influence the autonomic nervous system has recently been reported. Enteroendocrine cells of the gut epithelium were found to be in direct contact with mucosal neurons via a cytoplasmic process (Bohórquez DV, Shahid RA, Erdmann A, Kreger AM, Wang Y, Calakos N, Wang F, Liddle RA (2015) Neuroepithelial circuit formed by innervation of sensory enteroendocrine cells. *J Clin Invest* Jan 2. pii: 78361 doi:10.1172/JCI78361).

ACKNOWLEDGMENTS

Supported in part by the Michael J. Fox Foundation and the University of Louisville. The author is grateful to Drs. D. Demuth, K. LaFaver, P. O'Toole, R. Raha Chowdhury, A. Roberts, and V. Stribinskis for helpful comments and discussions. The author is also grateful to S. Nandi and J. Roberts for assistance.

The author's disclosure is available online (http://j-alz.com/manuscript-disclosures/14-2841r1).

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