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Advanced Innovative Amyloid Fibril Nanotechnological Applications: β-Sheet Proteins, Protein Aggregation, Cognitive Decline, Microbiome Regulated Tau Protein Release, Photo-Pharmacological Drug Regulation and Development of High Performance Surgical Adhesives

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Abstract

Amyloid self-assembled from amyloid peptides β-40 or β-42 is notorious due to the neurotoxic effects of β- oligomers in plaque and neurofibrillary tangles, neuronal dysfunction and diseases of cognitive decline such as Alzheimer's, or Parkinson's disease. This contrasts with so-called functional amyloids which are non-toxic ordered β-sheet molecular templates amenable to applications in tissue engineering. Long and hollow amyloid fibres, flattened tube and spiral ribbons have been used in engineering applications. Protein β-sheet core structures display diverse biological functionalities exploitable in futuristic self-assembling biomaterials revolutionizing nanotechnological developments in photopharmacology pain research, ultra-high performance surgical bioadhesives, and our understanding of amyloid fibril assembly. Use of nano-wires cast within hollow amyloid fibrils has advanced nano-electronics in next generation computers, biosensors, ultracapacitors, memristors, actuators and molecular switches. Amyloid fibrils have been used in photon capture light harvesting technologies in nano-photoelectronics, and photovoltaic photopharmacology futuristic nano-technological advances. A better understanding of amyloid fibril assembly processes may also uncover better ways to control the toxic build up of amyloid in brain tissues in diseases of cognitive decline. An innovative survey of over 1 million microbiome metabolites that regulate 300 G-protein coupled neuroreceptors and Tau microtubule dynamics show effects on amyloid fibrillogenesis. Some of these metabolites are absent in AD individuals prone to cognitive decline demonstrating the importance of the gut-brain axis in neuro-pathobiology. With the ever-expanding prevalence of cognitive diseases in ageing global populations a clear and present need exists to treat these conditions. A promising number of therapeutic interventions discussed herein warrant further exploration.

Keywords: Amyloid Fibrils, Nano-Electronics, Memristors, Biosensors, Photovoltaics, Photopharmaceutics, Microbiome Metabolites, GPCR Regulation

1. Introduction

This study has examined amyloid assembly processes in neurodegeneration to provide insights into how applications might be developed using β-sheet rich proteins in innovative assembly processes in the development of new generation biomolecular functional scaffolds in technological advances in nanobiology and in improved therapeutic manipulations of novel therapeutic compounds.

1.1. Definition of Amyloid and Amyloidogenesis

Amyloid is a historic generic term for insoluble misfolded protein aggregates with defining β-pleated sheet content that can undergo self-assembly through stacking of these β-structures. Amyloid can be stained with diazo Congo red dye through intercalation with these β-sheet assemblies and these exhibit a characteristic green-yellow birefringence under polarized light [1-6]. These misfolded proteins exhibit specific features that facilitate assembly of ordered repeat structures such as β-sheets, resulting in formation of insoluble amyloid deposits [1,5,6]. The importance of β-sheet secondary structure on the functional properties of β-sheet proteins has been evaluated using molecular dynamic simulations [7]. Innovative studies have identified that microbiome generated metabolites of dietary proteins transported to the brain can regulate G-protein coupled receptors (GPCRs) and control microtubule structure and hyperphosphorylation of Tau protein leading to its release from the microtubule to act as a nucleating factor in βA fibrillation dynamics [8]. Raman spectroscopy reveals that photo biomodulation can induce a transition of α-helix to β-sheet protein structures promoting neurodegenerative changes and development of Alzheimer's disease (AD) demonstrating the importance of β-sheet structures in degenerative brain pathology [9]. A greater understanding of this transitional process may reveal new therapeutic opportunities to treat diseases of cognitive decline.

The importance of β-sheet structures in Aβ fibril formation has been evaluated using molecular dynamics simulations [7]. Raman spectroscopy has also demonstrated transitional changes in tubulin structure and Tau protein organization that contribute to β-sheet and amyloid fibril assembly processes of likely importance in the development of AD [9]. Preferential binding of aromatic amino acids to Aβ42 occurs through pi or π-π stacking and hydrogen bonding. Oligomeric polypeptides (K8Y8, K4Y8, K8W8) containing Lys and the aromatic amino acids Trp or Tyr significantly decrease Aβ42 aggregation as determined by thioflavin T staining, CD spectra and molecular docking studies [10]. Cell viability assays with these blocking peptides also confirmed a significant reduction in the toxicity of Aβ42 on the SH-SY5Y neuroblastoma cell-line which has been used extensively in neurobiology [11]. A β-sheet breaker peptide HPYD (His-Lys-Gln-Leu-Pro-Phe-Tyr-Glu-Glu-Asp) has been designed that disrupts amyloid fibril assembly and has also been evaluated in behavioral testing studies and by transcriptional profiling [12]. Norepinephrine has also been shown to inhibit AD-β peptide aggregation and destabilizes AD-β protofibril formation [13]. Several studies have also reported on the synthesis of some short synthetic peptides called β-sheet breaker peptides which disrupt β-amyloid fibril assembly [14].

1.2. Assembly of Amyloid Fibrils, Plaques and Neurofibrillary Tangles

The Aβ peptides which form brain amyloid deposits are assembled into dimers, trimers, oligomers and distinctive fibrillar structures (Figure 1). All of these amyloid species share a common aggregation mechanism independent of the protein primary sequence progressing from amyloid monomers to formation of metastable soluble amyloid prefibrillar oligomers that eventually lead to stable insoluble mature amyloid fibres [15]. It is generally accepted that it is these pre-fibrillar amyloid oligomers which are primarily responsible for amyloid neurotoxicity in the brain rather than the monomers or mature fibres [16]. Generic amyloid deposits however can occur in many tissues in the human body, these involve a range of small misfolded proteins of variable β-sheet content but all lead to organ and tissue dysfunction [17,18]. Amyloid accumulation, plaques and neurotangles in the aging brain specifically lead to diseases of cognitive decline such as AD or Parkinson's disease (PD) [19-22].

1.3. The Deleterious Impact of Amyloid Deposition in Tissues

Amyloid plaques can be viewed using light microscopy employing a variety of staining methods including silver stains, Congo red diazo dyes, Thioflavin, cresyl violet and periodic acid-Schiff (PAS) procedures [17,24]. These stain different components in plaques and neurotangles, with variable sensitivity. Immunolocalization of amyloid plaques with a range of specific antibodies to Aβ epitopes and to other amyloid-associated components has also been undertaken [25]. Amyloid fibrils display diverse molecular structures, ENTAIL and PARROT are two bioinformatics systems that have been developed for the classification of amyloid fibril biodiversity. Ultrasensitive, new generation amyloid biosensors have also been developed for the detection of amyloid peptides in tissues, plasma and cerebrospinal fluid [26-36]. Amyloid plaque formation may be linked to trauma of the brain microvascular system, chronic brain inflammation and immune dysfunction [37-39]. Predictive algorithms have been developed to assess peptides with a propensity to form amyloid fibrils in web-based software that predicts aggregation-prone protein sequences [40-42]. AMYLPRED2 (http://biophysics.biol.uoa.gr/AMYLPRED2) is a public web predictive tool for amyloidogenic determinants in 'aggregation-prone' peptide sequences [41]. It should be stressed that it is well known that amyloid toxicity is mainly due to the amyloid prefibrillar oligomers but not to the amyloid monomers or mature fibres [16]. This is due to the disruption of membrane integrity by the oligomer pore forming properties that effect Ca^{2+} homeostasis [43-45]. Membrane depolarization in the neuron results in activation of voltage gated ion channels and regulated control of the influx of Ca^{2+} resulting in neuron activation. This influx of Ca^{2+} results in mobilization of neurotransmitters contained in synaptic vesicles which are transported in a coordinated fashion by SV2 proteoglycan to the synaptic gap regulated by Ca^{2+} sensitive glycoproteins such as the synaptotagmins [46]. Merging of the synaptic vesicles with the post-synaptic membrane results in release of these neurotransmitters into the synaptic gap where they are taken up by adjacent neurons in the neural network and neurotransmission occurs [47]. Ca^{2+} is thus an important cell regulator particularly in neural activation and neurotransduction in neural networks and in neuron-astrocyte communication. Ca^{2+} modulates calmodulin-dependent protein kinase kinase signal transduction and this is a central organiser of synaptic plasticity, learning and memory [48,49]. Uncontrolled entry of Ca^{2+} through Ca^{2+} channels however is also a cell death trigger in neurons and

astrocytes thus proper control of this Ca^{2+} influx is important to maintain neuron activity and viability [46,47]. Calcium dyshomeostasis drives pathophysiological and neuronal changes in neurodegenerative diseases aggravating the symptoms of AD through aberrant activation of neuronal networks and dysregulation of neuron-astrocyte signaling [50-53]. This results in deleterious impacts on synaptic and cognitive processes that contribute to neuronal dysfunction and the pathogenesis of AD [54].

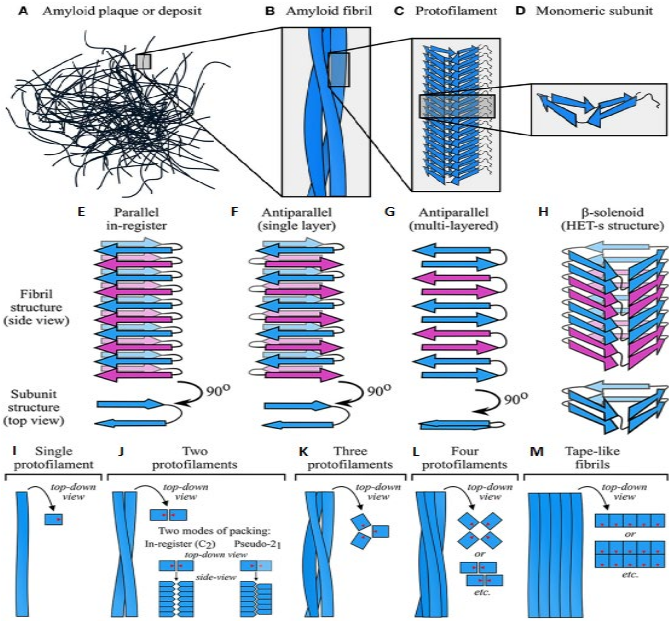

Figure 1: Schematic showing the hierarchical organization of amyloid microfibrils and how they are assembled into β-pleated sheet structures, amyloid plaques and neurotangles. The dominant components of amyloid plaques or deposits are amyloid fibrils (A, B) formed by close lateral association of protofilaments (C) formed by stacking of monomeric subunits (D).

Depiction of in-register cross-β structures (E), two intermolecular β-sheets are shown (F). In antiparallel cross-β structures, each subunit contributes a single β-strand per β-sheet, but the strand direction alternates (G). In multi-layered antiparallel structures, each subunit contributes more than one strand per β-sheet (H). In β-solenoids such as HET-s, subunits occupy more than one layer by coiling in solenoid like orientations, adjacent subunits are alternately colored blue and purple.

Schematic depictions of protofilament organizational forms. (I) single protofilament, (J) two protofilament twisted ribbon, (K) tubular structure formed by association of several protofilaments, often with rotational symmetry about the fibril axis (L), or a tape-like side-by-side association of protofilaments (M). Figure reproduced from under Open Access [23].

1.4. Not all Amyloids Induce Deleterious Functional Impacts on Tissues

In nature, amyloids have a range of functions across diverse organisms, ranging from mammals, bacteria, fungi and marine organisms [55-60]. So-called functional amyloids participate in an array of physiological processes such as regulation of pigment formation, storage and controlled release of peptide hormones, memory, fertilization of oocytes by sperm, antimicrobial responses, regulated necrosis, cellular responses to stress. Amyloid fibrils are also found as components in marine bioadhesives such as those which provide adhesion of barnacles and mussels to substrata. These have powerful adhesive properties that have inspired the development of tissue adhesives of potential application in highly specialized surgical procedures [59-70]. The unique architectural assembly processes and exceptional mechanical strength of amyloid fibrils makes these structures of interest in innovative applications in nano-electronics, and in development of suturing materials and vascular and orthopedic implants [71-76].

2. Amyloids as Attractive Candidates in Tissue Engineering

2.1. Natural Amyloid Fibrils

Functional amyloids are attractive biomaterial candidates for tissue engineering applications [77-79]. Amyloid fibrils undergo self-assembly, forming regularly organised structures with impressive biophysical properties and a range of morphologies including extended straight filaments, tapes, twisted ribbons, and hollow tubes. Fibrils are typically 5–20 nm in diameter with a length in the micron size range.

2.2. Synthesis of Amyloid Fibrils in the Laboratory

Fibrils can also be assembled from a diverse range of small proteins and polypeptides over a wide range of assembly conditions influenced by temperature, pH and solvent conditions providing flexibility in the procedures that may be utilised in engineering applications to assemble fibrils at the nanoscale level. Furthermore, fibrils are assembled from arrangements of amino acids amenable to genetic manipulation and a range of biosynthetic bacterial protein expression systems are available. Introduction of point mutations in fibril proteins can introduce design features which vary chemical and electrostatic fibril surface characteristics which modulate binding properties and responsiveness to unique environmental conditions [80,81].

3. The Versatility of Amyloid Fibrillar Forms

Several classes of engineered amyloid polymers have been developed with impressive credentials as biomaterials for engineering applications. These include (i) templates for casting of silver or gold nanowires used in nanoelectronics, (ii) hydrogels and bioscaffolds for delivery of stem cell and therapeutic drugs, (iii) light harvesting electron transport biomaterials for biophotonics, (iv) biosensors, actuators and molecular switches [82,83].

Hollow ~100 nm nanotubes have been developed using self-assembly of amyloid-like fibrillar structures to form templates within which silver nanowires can be cast of 10-nm width and lengths ranging from 60 to 100 microns [84-86]. The central nanowire is subsequently recovered by proteolytic digestion of the peptide shell. Multi-layered co-axial nano-wire assemblies have also been prepared decorated on the exterior of the nanowire

with metallic gold as confirmed by TEM and energy dispersive X-ray analysis. Gold or silver nanowires with widths of ~100 nm with demonstrated high conductivities and low resistances (~80 Ω) have been applied in nano-electronics revolutionising the development of next generation computers and biosensors [87,88]. Ultracapacitors have also been developed using an external magnetic field to orient horizontal and vertically aligned arrangements of nanotubes. These amyloid assemblies display enhanced capacitance relative to carbon and carbon nanotube–modified electrodes [89].

3.1. Amyloid Fibril Applications in Nano-Electronics

Silver and gold nano-wires have found application in nano-electronics in the development of actuators, molecular switches and memristors in microcomputing [85-87,89-95]. The memristor is a resistor with memory that behaves similarly to biological synapses [96]. The low power requirements and ultra-high speed signal transmittance capability of memristors is revolutionising development of neuromorphic circuits that are used in synthetic neural networks, switching devices and low-power sensors in microcomputing [97-99]. Nano-wires cast using hollow amyloid fibrils as casting templates have been used in bio-sensing, optoelectronics and photovoltaics and show potential in the development of synthetic synapses in highly innovative bio-nanotechnological applications [100-102]. Furthermore, carbon-nanomaterial-amyloid fibril hybrids have potential uses in organic micro-electronics and bio-sensing in biomedicine and in structural nano-biomaterials. Amyloid fibrils have been used in a number of applications in tissue engineering [78]. Photobiomodulation therapy, using near infra-red 700-1400 nm low-level laser phototherapy, reduces the deposition of beta-amyloid in the AD brain, ameliorating neuroinflammation and oxidant stress, supporting mitochondrial homeostasis to elicit a healing or regenerative response [103]. The surface chemistry of engineered amyloid fibrils can be modified depending on the amino acids employed and bacterial protein expression systems used. Furthermore, amyloid fibrils can be coated with chemicals such as, poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT-S), luminescent polyfluorene (PPF) or ammonium pentadecafluorooctanoate (APFO) that modify their responsiveness to specific chemical microenvironments [104-106]. Fibrils can also be coated with gold nanomaterials modified with peptides or other chemicals. Gold itself is chemically inert but highly conductive and, when modified with additional components, can fine-tune the surface interactivity of amyloid fibrils. Some chemicals (PEDOT-S, PPF, APFO) can improve the light harvesting and electron transfer properties of fibrils which can improve the efficiency of photobiomodulation therapy [107]. Other amyloid fibrils can display catalytic enzymatic properties with hydrolases, esterases, lipases that can be harnessed using the fibril as a nanoscaffold for enzyme immobilisation in biosensors or to develop enzymatic activities that disassemble insoluble amyloid deposits [83,107-109].

3.2. Use of Amyloid Fibrillar Assemblies in Neuromorphic Computing

Quantum computers offer the computational power required to drive neuromorphic hardware in neural network dynamic simulations [110]. Machine learning and artificial intelligence algorithms running on neuromorphic hardware are being developed to assist in data analysis in artificial synapse modular supercomputing developments. Self-assembling amyloid fibrillar structures can be modeled to provide neuromorphic hardware due to varied fibril surface chemistry and their responsiveness to specific electrochemical microenvironments. This may be useful in the development of electrochemical random-access memory using ionic neurotransistors, leading to neuromorphic computing networks that drive sensory intelligent perception systems [111,112]. Application of AI methodology in brain-interface technologies offers particularly exciting possibilities in the improvement of real-time bidirectional control systems between living brains and actuators in motor and sensory neuromorphic applications and have already had notable clinical success in the treatment of paralyzed patients' and expanded the mobility of disabled patients [113].

3.3. Development of Suturing Material and Vascular and Orthopedic Implants Using Amyloid Polymers

The mechanical strength of amyloid fibrils Amyloid fibrils possess a Young's Modulus in the GPa scale and a strength comparable to steel. High-resolution data gathered from X-ray diffraction and NMR experiments, demonstrate an extensive cross β-sheet content within the core of the fibril forming an expansive hydrogen-bonding network spanning the length of the fibril. It is this cooperative intermolecular hydrogen-bonding network which confers stability and unique material properties to amyloid fibrils [114,115]. Amyloid fibrils have similar mechanical properties to dragline spider silk, which is one of the strongest and most rigid biomaterials in nature [71]. Silk and amyloid fibrils both contain expansive hydrogen-bonded β-sheet networks. The material properties of amyloid fibres and β-sheet rich silk proteins makes them attractive candidates for the development of suturing materials and orthopedic and vascular implants for tissue repair. The β-sheet content of structural proteins produces very stable structures through lateral inter-chain hydrogen bonding. Silk fibroin is a good example of a block co-polymer structure with β-sheet content which provides high tensile strength (0.5~1.3 GPa) and toughness (6 x 104~16 x 104 J/Kg) and is responsible for the strength of spider web drag-line silk [72-76]. Elucidation of the hierarchical structural organisation of silk fibers shows these are similar to amyloid fibrils and illustrates how silks unique mechanical features are achieved and how silk outperforms animal horn material in terms of strength and toughness [116,117]. High strength hydrogels can also be prepared using silk fibroin as a scaffolding material [118]. Vascular patch implants based on silk have also been developed and functionalized with perlecan, an angiogenic proteoglycan to improve vascular biointegration [119,120].

3.4. Customised Amyloid Fibrils Made in the Laboratory

While natural self-assembled amyloids are nanometer-sized fibrillar biomaterials, it is now possible using in-vitro methods to assemble large 10-20 α m diameter amyloid fibers several mm in length [121]. Using a short, hydrophobic director α-helical template peptide and mixtures of peptides it is possible to self-assemble large amyloid fibers, encoded by micron-sized self-assembled structures at the genetic level, with tailored rectangular or cylindrical cross-sectional morphologies and robust material properties (modulus 0.1-2.5 GPa) [122-123].

3.5. The Versatility of Amyloid Hydrogels and Bioscaffolds

The ECM has important instructive properties over cells encoded in peptide epitopes of structural and signaling ECM components that act as molecular directors of cellular activity [124]. Peptide epitopes can be incorporated into synthetic amyloid biomatrices to mimic the specific communication that occurs between cells and tissues to control cell adhesion, differentiation, immunomodulation and ECM turnover to achieve tissue homeostasis [125]. Cell adhesion on amyloid fibrils occurs despite a lack of integrin recognition motifs, biomatrices have also been prepared containing RGD cell attachment motifs to further improve cell attachment providing versatile biomaterials for tissue engineering applications including the culture of neurons and to develop a model of AD [126-133]. Amyloid fibril bioscaffolds have been used to culture neural progenitor cells to assess if an Aβ β-sheet environment guided differentiation of cultured neural progenitor cells simulating conditions found in brain tissues in which amyloid deposition occurs. Aβ β-sheet bioscaffolds produced neural progenitor cells of a phenotype similar to that induced by amyloidosis in AD tissues [134].

4. Innovative Biotherapeutic Applications of β-Sheet Proteins in Biomedicine

4.1. Developments in Light Harvesting Technology in Photo-pharmacology

Amyloid fibrils have Ultraviolet–visible–near-infrared optical light capture properties and have been applied to study the mechanism of amyloid fibril formation and in healthcare applications [135-136]. Light capture technologies have also been applied in the activation of photoswitchable drugs in the regulation of neural pain generation. A problem of systemic pharmacotherapeutic neuroinhibitory medications like antiseizure drugs, which are used to treat epilepsy and neuropathic pain is off-target activity, which can cause unwanted side-effects. There is an urgent need for drugs that effectively inhibit nerve signals locally to alleviate pain without unwanted side-effects. Photopharmacology uses light-activated drugs illuminated locally at specific tissue target sites to provide specificity of action. Photoswitchable derivatives (carbazopine-1, carbadiazocine) of the antiseizure drug carbamazepine (tegretol) have been developed to treat tonic-clonic seizures and bipolar disorder and to relieve the intense, stabbing, electric shock-like pain caused by trigeminal neuralgia (douloureux, Fothergill disease). Carbadiazocine can be photoswitched between 400-590nm using light emitting semi-conductor diodes (LEDs) to activate specific analgesic mechanical and thermal pain relief profiles in a rat model of neuropathic pain [137]. Engineering of amyloid fibril optical biosensors using smart Trojan-horse technology can potentially improve light delivery precision in tissues to photoactivatable drugs offering innovative light harvesting technology solutions in photomedicine [136,138-142]. These types of drugs have also been examined for the detection and eradication of β-amyloid fibril deposits in tissues [143].

4.2. Development of Innovative High Performance Surgical Adhesives Based on β-Sheet Block Co-Polymer Proteins

Surgical wound closure has traditionally been undertaken using suturing techniques. However, some wound margins in very soft tissues are not mechanically strong enough to adequately support such a closure method. Biological adhesives or glues represent an alternative closure method and have added advantages since the absence of suture sites removes potential sites of biological infection or regions of point loading which may lead to tissue tearing and sites of infection in very soft tissues [61]. Catechol block co-polymer chemistry in marine (mussel, barnacle) adhesives and insect structural proteins have shown great potential in the development of ultra-strong wet-set tissue adhesives and these proteins only illicit a mild immune response [144-148]. Pvfp-5β folds as a β-sheet-rich protein which stacks in a catechol based repeat co-polymer resembling amyloid β-fold stacked protein structures [149,150]. Silk fibroin also displays similar block co-polymer organization in ultra-strong insect proteins such as spider-web drag-line silk [151]. Pvfp-5β folds as a β-sheet-rich protein containing repeat EGF-like modules and this polymer has strong adhesive properties on glass and plastic and no cyto-toxic side-effects [149,150]. Engineering of mussel adhesive proteins containing L-3,4-dihydroxyphenylalanine (DOPA) cross-linked with lysine can increase their β-sheet contents providing polymers with improved gradual silver release properties and toughness [152]. These polymers have excellent antibacterial properties against Gram-positive Staphylococcus aureus and Gram-negative Escherichia coli further improving the performance of such polymers in surgical procedures. Furthermore, anti-bacterial silk-fibroin scaffolds containing silver nanoparticles increase osteoblast proliferation and human mesenchymal stem cell differentiation and have been used in bone regenerative procedures [153-155]. Bioadhesive protein polymers with programmable material properties can be engineered in the laboratory. Increasing the silk amyloid content of these polymers enhances the β-sheet content and toughness of such polymers [156]. The wet adhesive properties of such polymers are also tunable through defined molecular interactions [157-159]. Furthermore, an engineered biocompatible hydrophobic light-activated adhesive has been developed based on mussel DOPA adhesive [160]. The powerful adhesion this polymer provides to wet tissue within seconds of light application has been applied to high-pressure large blood vessels and cardiac wall defects [161,162]. Interventricular adhesive patches have been used in a beating porcine heart with sufficient adhesive strength to resist supraphysiologic pressures for 24 h providing immediate hemostatic repair of vascular surgical defects and offer

instantaneous adhesion. This adhesive has impressive credentials in tissue closure in demanding areas of surgical intervention.

Amyloid fibrils have also been observed in adherent marine organism adhesive compounds that contribute to their astonishing adhesive strength, tenacity of binding and very rapid adhesive properties under adverse environmental binding conditions [55,115,163,164]. Such polymers in barnacles and mussels have been de-engineered and new polymers created, inspiring the development of a new generation of high-performance surgical adhesives. These may obviate the need for sutures in demanding surgical procedures in very soft tissues where sutures may not hold adequately and may be a potential site where tearing of suture sites can increase the likelihood of microbial infection [61,165,166]. Surgical bioadhesives based on amyloid are non-immunogenic and may obviate the need for sutures altogether, providing improved healing responses in cardiac surgery and can even be used directly on the beating heart where their rapid, exceptional tissue adhesive properties are an important innovative surgical application [167].

Amyloid fibrils also occur in high performance structural insect proteins. Spider-web drag-line and aquatic silk fibroin copolymers in silk-moth (Bombyx mori), caddis-fly larvae (order Trichoptera) and sandcastle worms (Phragmatopoma californica) have assembly properties similar to those in brain amyloid fibril formation based on modular silk-homology repeat motifs and β-sheet formations which promote formation of block co-polymers [79,168]. Silk proteins have found application as suturing material and the preparation of engineered composite constructs used in biomedicine [61].

4.3. Microbiome Metabolites with GPCR Instructive Roles Promoting Tau Protein Release from Microtubules

Innovative gut microbiome research has shown how microbiome generated metabolites can regulate GPCRs influencing Tau protein aggregate assembly processes that affect development of Alzheimer's disease. The gut microbiome is an innovative area of intense investigation that provides insightful clues into how amyloid assembly processes and neurosignaling may be influenced by dietary components processed by gut microbes and which can be transported by the vagus nerve of the gut-brain axis to the brain through the blood-brain-barrier [169-176]. These metabolites can modulate the development of protein aggregates assembled by neurons that mediate the pathogenesis of AD and offer potential novel opportunities to treat this condition [19,177-179]. Roles for the gut brain axis have been established in the potential regulation of neurodegenerative processes [8,180]. Metabolites generated by several members of the gut microbiota can efficiently activate host GPCRs and influence host physiological processes [181]. Many bioactive metabolites act through the engagement of GPCRs [182]. A highly multiplexed bioactivity screening technology has been developed to construct a GPCR interactome based on >300 GPCRs and 1,041 human microbiome generated metabolites from 435 microbiome populations [183]. GPCRs control neuronal excitability, synaptic transmission and plasticity, and cellular behavior through spatiotemporally controlled precise initiation of a variety of cell-signaling pathways. Astrocytes, oligodendrocytes, neurons and cerebrovascular endothelial cells all express A1 and A2A GPCRs and these can also participate in heteromeric interactions with adenosine A1, dopamine D2, or cannabinoid CB1 receptors [184]. Individuals with AD harbor different gut microbiomes compared to healthy people [8,180] and often lack bacterial species, such as Eubacterium rectale and Ruminococcus and consequently lack bacterial molecules produced by these microbes that are commonly found in healthy patients [8]. Computational modeling of potential interactions between one million microbiome generated metabolites and a number of neural receptors such as GPCRs has identified microbiome metabolites that reduce phosphorylated tau levels in AD neurons in healthy individuals [185-189]. Tau normally stabilizes the cytoskeleton that controls cell shape but in AD abnormal phosphorylation of tau results in its dissociation from microtubules, resulting in destabilization of microtubules and alteration in cellular activity. Furthermore, release of tau peptides can seed assembly processes for insoluble pathological amyloid protein aggregates in the brain [189]. N-acetylated and C-amidated AcPHF6 tau hexapeptide can cause significant acceleration in Aβ40 and Aβ42 fibril growth so it is important to better understand and control microtubule dynamics and this may facilitate development of more efficient inhibitory peptides that control fibril dis-assembly processes [190]. By combining machine learning and multi-omics the relationship between gut metabolites and GPCRs has been established and a GPCRome AD database has been constructed. This computational method and AI is a powerful systems biology approach that has been applied to identify microbiome directed personalized therapies by targeting the GPCRome and the contribution of β-sheet proteins in the pathogenesis of AD [8].

5. Conclusion

This review has shown that functional amyloids can be used to form versatile cell attachment matrices and hydrogels for cell delivery in tissue repair strategies and in innovative nano-electronics, bio-sensors, memristors and light harvesting technologies in photovoltaics and in photopharmacology. Ultra high performance β-sheet protein adhesive polymers have also been developed for specific highly demanding surgical applications. New developments show gut microbiome processing of dietary components produce metabolites with the ability to regulate GPCRs in the brain which regulate a range of physiological processes including the release of Tau protein peptides from microtubules with the potential to influence amyloid assembly processes and pathogenesis of diseases of cognitive decline. This opens a new potential therapeutic avenue for the treatment of these disabling conditions.

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