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Chapter 6

Pathogenic Angiogenic Mechanisms in Alzheimer's Disease

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Abstract

Vascular dysfunction is a crucial pathological hallmark of Alzheimer's disease (AD). Studies have reported that beta amyloid (Aβ) causes increased blood vessel growth in the brains of AD mouse models, a phenomenon that is also seen in AD patients. This has given way to an alternative angiogenesis hypothesis according to which, increased leakiness in the blood vessels disrupts the blood-brain barrier (BBB) and allows unwanted blood products to enter the brain causing progression of disease pathology, promoting amyloid clumping and aggregation along with impaired cerebral blood flow. Furthermore, the expression of melanotransferrin in AD model and patients may contribute to angiogenesis. The objective of this chapter is to attempt to establish a link between the vascular damage and AD pathology. Curbing the vascular changes and resulting damage seen in the brains of AD model mice and improving their cognition by treating with FDA-approved anti-angiogenic drugs may expedite the translational potential of this research into clinical trials in human patients. This direction into targeting angiogenesis will facilitate new preventive and therapeutic interventions for AD and related vascular diseases.

Keywords: Alzheimer's disease, amyloid beta, blood-brain barrier, angiogenesis

1. Introduction: history of vascular dysfunction in Alzheimer's disease

Alzheimer's disease (AD) presents itself as a progressive neurological disorder, which is the major cause of dementia leading to death in the elderly. It affects thinking, orientation and memory, causing impairment in cognition, social behaviour and motivation [1]. Approximately 47.5 million people worldwide have dementia, of which the most common contributor is AD with 60–70% [1]. In 2010, the total global societal costs were estimated to be US $604 billion corresponding to 1.0% of the worldwide gross domestic product [1].

In 1906, Dr. Alois Alzheimer [2] noted two microscopic neuropathological findings, which were further characterized and eventually established as the hallmarks of AD: senile neuritic plaques, which are aggregates that are primarily composed of beta-amyloid (Aβ) peptides; [3, 4] and neurofibrillary tangles, which are primarily composed of intra-neuronal hyperphosphorylated tau aggregates [5]. Aβ, a 4 kDa peptide, is a proteolytic cleavage product of the amyloid precursor protein (APP) by the action of α and γ secretase enzymes [6, 7]. Mutations either in the *APP* gene or in the secretase enzyme complex lead to a β secretase cleavage, forming a pathogenic Aβ species (Aβ1-42). These Aβ molecules aggregate to form oligomers, which multimerize into protofibrils, followed by the formation of dense core amyloid plaques [8–10].

1.1. Initial clinical observations linking AD and vascular disease

Post-mortem analysis has established that 50–84% of the brains of persons, who die aged 80–90+ years, show appreciable cerebrovascular lesions and although there is a debate around their impact on AD pathology, it is suggested that the independent dementia caused by vascular and AD-type pathologies may have additive or synergistic effect on cognitive impairment [11]. Vascular pathologies that have been seen in the aged human brain include: cerebral amyloid angiopathy (CAA), cerebral atherosclerosis, small vessel disease in most cases caused by hypertensive vasculopathy or microvascular degeneration, blood-brain barrier (BBB) dysfunction causing white matter lesions, microinfarctions, lacunar infarcts and microbleeds [11]. Studies in post-mortem of human brains also found evidence of increased angiogenesis in the hippocampus, midfrontal cortex, substantia nigra pars compacta, and locus coeruleus of AD brains compared to control brains suggesting that vascular dysfunction is an inherent part of AD pathology [12, 13].

1.2. Genetic risk factors linking AD and vascular disease

Epidemiological studies have identified risk factors for AD that are similar to those for cardiovascular disease (CVD) [14] such as hypertension during midlife, diabetes mellitus, smoking, apolipoprotein E (APOE) 4 isoforms, hypercholesterolemia, homocysteinemia and, in particular, age [1]. Familial AD is caused most commonly by presenilin 1 (*PSEN1*) or presenilin 2 (*PSEN2*) mutations. It is also seen that the presenilins are expressed in the heart and are critical to cardiac development. The work by Li *et al*. indicated that *PSEN1* and *PSEN2* mutations are associated with dilated cardiomyopathy (DCM) and heart failure and implicate novel mechanisms of myocardial disease [15]. Amyloid is a known vasculotrope and an

http://dx.doi.org/10.5772/66403

increased amyloid aggregation in AD brains is seen to be in interaction with the angiogenic and CAA positive vessels [14]. Apolipoprotein 3 (APOE3) is responsible for normal lipid metabolism; however, the APOE4 isoforms is strongly associated with the late onset of AD [13]. Carriers of this isoform show a decreased cerebral blood flow and have also been linked to disorders associated with elevated cholesterol levels or lipid derangements (*i.e.* hyperlipoproteinemia type III, coronary heart disease, strokes, peripheral artery disease and diabetes mellitus) [15]. These overlapping genetic risk factors might give us a direction for understanding the mechanisms of the disease-related pathways.

1.3. Factors linked to AD and increased angiogenesis: melanotransferrin (p97), VEGF, transglutaminases (factor XIIIa and tTG)

Melanotransferrin (also known as p97 or melanoma tumour antigen) is a member of the transferrin family and is responsible for the cellular uptake of iron. P97 was shown to be present in the capillary endothelium in a normal brain, in contrast to the brain from patients with AD, where it is found to be localized in microglia cells, associated with senile plaques [16, 17]. Serum normally contains very low levels of p97; however, it is reported to increase by five- and six-fold in patients with AD [18, 19]. From this observation, it was proposed that serum p97 could be a potential biochemical marker for this disease. It was further demonstrated that melanotransferrin exerts an angiogenic response quantitatively similar to that elicited by fibroblast growth factor 2 [20], and hypervascularity has been shown to be a feature in the brains of AD patients [12]. Overexpression of vascular endothelial growth factor (VEGF) receptor 2 was observed in newly formed vessels, suggesting that the angiogenic activity of melanotransferrin may depend on activation of endogenous VEGF [20]. VEGF is the major player in pathological/dysfunctional blood vessel formation. It is shown that VEGF is highly up-regulated in AD brains via the inflammatory pathway and also that VEGF co-aggregates with Aβ in AD brains [13]. The role of transglutaminases in AD is highly debated; however, it is shown that the activity of these enzymes might contribute to both angiogenesis and in the formation of protein aggregates in the AD brain [21, 22].

2. Alzheimer's disease and the blood-brain barrier pathogenesis: angiogenesis and inflammation

A physical seal is present between the vasculature in the brain and the central nervous system that restricts fluid and entrained molecules from being transported into the brain from the systemic circulation [13, 23]. Dysfunction of the BBB was originally seen in animal models of AD [24] and was later established as a prominent, but unexplained clinical feature of AD in patients [23]. Though it is unknown where the BBB dysfunction stems from, it is, however, argued that Aβ may be directly involved in this process [25, 26]. Leakiness of the BBB has been demonstrated in a number of AD transgenic animal models that have overexpression of *APP*, including the Tg2576, which manifests a form of early-onset AD [24, 25]. Studies show that BBB integrity is compromised in this mouse model as early as 4 months of age, much before

the onset of other disease pathology, such as the consolidated amyloid plaques [24, 27]. Hence, the mechanism leading to the BBB disruption is a potential target for AD therapy.

2.1. Tight junction disruption in mouse models

The brain has a unique structure termed as the blood-brain barrier (BBB), which is a specialized physical seal that precludes the transport of various, large and/or hydrophilic, peripheral blood molecules from entering the brain parenchyma [13, 25]. This restricted exchange protects the brain from indiscriminate exposure to peptides, macromolecules and potentially toxic molecules [13, 25]. The integrity of the BBB is maintained by inter-endothelial complexes called tight junctions (TJ), in the brain capillaries, that are composed of a variety of plasma membrane spanning proteins (occludin), scaffold proteins (zonula occludens protein-1; ZO-1) and the actin cytoskeleton [12, 13, 25]. The peripheral membrane protein, ZO-1, localizes along blood vessels in the brain parenchyma and along with claudins and occludin ensures the intactness and permeability of the BBB [26, 28]. A second barrier is presented by the basal lamina, composed of type IV collagen, fibronectin and heparan sulphate along with other molecules, which operates as a molecular weight filter [26]. Lastly, there are cells that interact to protect the BBB, known as the neurovascular unit (NVU). This is composed of neurons, cerebral endothelial cells, basal lamina, astrocytic foot processes (containing proteases and neurotransmitters) and perivascular macrophages called pericytes [26].

Since the BBB plays crucial role in maintaining central nervous system (CNS) homeostasis, its dysfunction proves deleterious for the smooth working of the brain. The BBB dysfunction includes: (1) BBB disruption, resulting in the discharge of potentially neurotoxic circulating substances into the CNS; (2) transporter dysfunction, which consequently creates deficiency of nutrient supply and amplify toxic substances in the CNS; and (3) altered protein expression and NVU cell secretions, potentially resulting in inflammatory activation, oxidative stress and neuronal damage [28]. The three effects stated above have been reported in AD patients, although the scope of this chapter pertains only to BBB disruption.

The compromised integrity of the BBB has been indicated by increased CSF/serum albumin ratios seen in AD patients [28]. Albumin is a macromolecule that is unable to cross an intact BBB [27, 28]. Histological studies have also revealed the presence of albumin staining around microvessels that shows co-localization of amyloid plaques and angiopathy [12, 13, 26]. It is suggested that this staining is a result of an affinity of extravasated albumin for amyloid [28].

Prothrombin is seen at elevated levels particularly around the microvessels in the brains of AD patients [29]. Highest levels of the protein were observed in people scoring higher in the Braak staging [30, 31].

The increased vesicularization of brain endothelial cells damages the BBB by altering the tight junction function. This is consistent with increased transcytotic disruption of the BBB initiated by the release of inflammatory cytokines that are angiogenic triggers, promoting paracellular leakage [28].

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2.2. CBF impairment: a road to hypervascularity in mouse models and humans

Vascular dysfunction is a crucial pathological hallmark of AD [12, 32]. The two key precursors to neurodegenerative changes and Aβ deposition in AD are the BBB breakdown [12, 32] and cerebral blood flow (CBF) impairment [33]. Various studies with the help of a non-invasive imaging technique (arterial spin labelling MRI) have shown that AD is associated with a global, as well as a regional CBF impairment, also known as cerebral hypoperfusion [34]. While AD patients exhibit a global decrease in blood flow (averaged 40%), compared to healthy controls, the CBF reduction is seen only in specific regions that are usually implicated in the disease state [14, 34]. It is, however, argued whether a diminished blood flow in AD is a cause or consequence of the disease.

Hypoperfusion is associated with both structural and functional changes in the brain and hence plays a pivotal role in influencing the permeability of the BBB [34]. Severe reductions in CBF have been seen in the elderly at a high risk for cognitive decline and AD [34]. Individuals that are carriers of the major AD risk allele, (APOE4), have a more impacted regional deteriorated CBF than non-carriers of the allele [35, 36]. AD-related vascular pathology impairs cerebral autoregulation and causes cerebrovascular insufficiency [37]. This impaired CBF and compromised BBB result in the accumulation of potentially neurotoxic molecules (*e.g.* increased Aβ concentration) in the brain along with the entry of unwanted blood products via peripheral circulation [38, 39]. Data obtained from structural MRI scans show atrophy in different regions of the brain, and an overall change in cortical thickness is observed due to hypoperfusion in AD patients [34]. The thickness of the cortex is an important predictive measure of evolution to AD for subjects with mild cognitive impairment [34]. Carriers of the APOE4 allele, a demographic reported to have glucose hypo-metabolism, demonstrate hastened cortical thinning in areas most vulnerable to aging (medial prefrontal and peri-central cortices) as well as in areas associated with AD and amyloid-aggregation (*e.g.* occipito-temporal, basal temporal cortices and hippocampus) [34]. Ageing is the leading risk factor for the development of late-onset AD. Aberrations in vascular ultrastructure, vascular reactivity, resting cerebral blood flow and oxygen metabolism are all associated with age and act as a catalyst for cerebrovascular diseases and subsequent cognitive deficits [40]. To cope with the decrease in blood flow, the brain has evolved a compensatory mechanism whereby it increases the formation of blood vessels resulting in hypervascularity, a phenomenon which is seen not only in mouse models [40–43] but also in post-mortem samples of AD patients [43].

2.3. Involvement of angiogenesis and not apoptosis

The 'vascular hypothesis' as stated currently, defends that the vascular damage is a consequence of diminished blood perfusion of the brain, leading to hypoperfusion/hypoxia causing the BBB dysfunction [44]. A subsequent amalgamation of accumulated Aβ, neuro-inflammation, and the eventual disintegration of the neurovascular unit is seen, culminating in vascular death [13, 25, 45]. In a state of hypoperfusion, the hypoxia-inducible factors initiate angiogenesis (the formation of blood vessels) through the up-regulation of pro-angiogenic factors [25]. The main player in this blood vessel formation is VEGF, which induces differentiation and proliferation of endothelial cells from its progenitors, the hemangioblast and the angioblast

[46]. This forms an inefficiently differentiated primitive vascular plexus (vasculogenesis) [47]. The vascular plexus undergoes remodelling, that is triggered by the angiopoietin-1 (Ang-1), into a hierarchically structured mature vascular system established through endothelial cell sprouting, trimming differentiation and pericyte recruitment (normal angiogenesis) [48]. In contrast to these events in AD, it is observed that, a downstream cell signalling molecule to VEGF, angiopoietin-2 (Ang-2), destabilizes the vessel wall of mature vessels [32, 49–51]. The quiescent endothelial cells become sensitive to VEGF (and other angiogenic factors), proliferate indiscriminately, migrate to form new vessels that are not able to mature and eventually lead to the establishment of a leaky network of blood vessels [32]. This phenomenon is termed as pathological angiogenesis, which is a common occurrence seen during the evolution of tumours. In accordance with the current version of the 'vascular hypothesis', the BBB disruption is due to vascular cell death caused by apoptosis and angiogenesis would only be required to ensure tissue regeneration and likely be limited to replacing the damaged tissues and ensuring oxygenation of brain tissues [12, 13]. However, this role of apoptosis in BBB dysfunction is highly debated. Recent studies have shown that endothelial cell proliferation, during pathological angiogenesis, results in hypervascularity [12]. As a compensatory mechanism to the decreased blood flow caused by the leaky blood vessel network, vascular remodelling and structural changes take place in the physical arrangement of the tight junction proteins, resulting in compromised BBB integrity [12, 52]. The work of Biron *et al.* characterized the relationship between amyloidogenesis and BBB integrity, through changes in the TJ morphology in the Tg2576 AD mouse. They reported that the Tg2576 AD mice exhibit no apparent vascular apoptosis but have significant TJ disruption, which was seen directly linked to pathological angiogenesis, resulting in a significant increase in vascular density in AD brain [12]. Hence, it can be said that these data support the model that TJ disruption results from increased vascular permeability that takes place during extreme neovascularization in AD.

2.4. Angiogenesis: inflammation and vascular activation

Increasing evidence suggest that the vascular perturbation appears as a common feature in AD pathology as its hallmarks: amyloid plaques and neurofibrillary tangles. Over the years, emphasis has still been given to the accumulation of Aβ in AD, which, as a result of its impaired clearance from the brain, is thought to be responsible for the onset of cognitive decline [39, 53–55]. Paradoxical to this hypothesis, aggregated Aβ can be extensively present in the human brain in the absence of AD symptoms [56–58]. Although Aβ plays a crucial role in AD, it is neither necessary nor by itself sufficient to cause full AD pathology [27]. The alternate idea is that the mere production of Aβ (amyloidogenesis), promotes extensive pathological angiogenesis, leading to the redistribution of TJs, which then causes disruption to the BBB integrity, thereby increasing vascular permeability, subsequent hypervascularization and eventual AD pathology. This alternate 'vascular hypothesis' stems from a body of data that now establishes hypervascularization as a mechanistic explanation for amyloid-associated TJ pathology [12]. It provides new modalities for therapeutic intervention that target the restoration of the BBB by modulating angiogenesis, thereby possibly preventing AD onset and potentially repairing damage in the AD brain. A second study by Biron *et al.* demonstrated that immunization with Aβ peptides neutralized the amyloid trigger that causes pathological angiogenesis and thereby

http://dx.doi.org/10.5772/66403

reverses hypervascularity in Tg2576 AD mice [59]. The Aβ plaques were seen to be dissolved, solubilized Aβ removed from the brain parenchyma along perivascular drainage routes, which resulted in a decrease in the hypervascularity [59]. This supports a vascular angiogenesis model for AD pathophysiology and provides the first evidence that modulating angiogenesis repairs damage in the AD brain.

Pathological angiogenesis and hypervascularization in an AD brain occurs in response to impaired cerebral perfusion (oligaemia) and inflammatory response to vascular injury [60]. We have already discussed the impaired perfusion in Section 2.2. In this section, we will look at the inflammatory activation of angiogenesis. Morphological and biochemical evidences present themselves in the form of regionally increased capillary density, unresolved vascular sprouting, glomeruloid vascular structure formation, and up-regulated expression of angiogenic factors: VEGF, transforming growth factor β (TGF β) and tumour necrosis factor α (TNF α) [60]. In AD, inflammatory pathways, when stimulated, cause the release of angiogenic cytokines such as thrombin and VEGF, contributing to pathological angiogenesis [60]. It is hypothesized that a thrombogenic region develops in the endothelial cells of the vessel wall, leading to intra-vascular accumulation of thrombin. This thrombin activates the vascular endothelial cells to secrete amyloid precursor protein via a receptor-mediated protein kinase C-dependent pathway [60]. Progressive deposition of amyloid precursor protein leads to accumulation of the Aβ plaques, which generates more reactive oxygen species and induces further endothelial damage in a cycle of neurotoxic insult. This establishes a cycle of neurotoxicity and death, instituted by the discharge of thrombin following Aβ-induced neuroinflammatory responses [60]. Other studies further support the interaction of Aβ with thrombin and fibrin throughout the clotting cascade, to increase neurovascular damage and neuroinflammation [61–63]. Astrocytes, cultured *in vitro* and stimulated with Aβ, showed a release of neuroinflammatory cytokines that resulted in the increased expression of VEGF [49, 50]. Other pro-inflammatory cytokines, such as interleukin-1β are increased during AD and known to induce VEGF and growth of new blood vessels [52, 64].

Consequential evidence is present implicating Aβ as a vasculotrope, modulating blood vessel density and vascular remodelling through angiogenic mechanisms. Brain microvessels have been shown to be closely associated with Aβ plaques with the aid of ultrastructural studies. It was observed that that AD brain capillaries contained pre-amyloid deposits [60]. Aβ stimulates angiogenesis in a highly conserved manner, which is speculated to be mediated through γ-secretase activity and Notch signalling [60, 65]. The *in vitro* studies of human umbilical vein endothelial cells (hUVEC), exposed directly to Aβ1-40 and Aβ1-42, show an angiogenic effect on the hUVEC, which exhibited an increase in the number of tip cells and branching [60].

The indication for Aβ-related angiogenesis has been extended *in vivo* as well, which can be observed with the chick embryo chorioallantoic membrane assay [65]. Aβ1-40 and Aβ1-42 stimulated embryos illustrated escalated vascular growth [65]. *In vivo* studies, using various APP mutant AD mouse models that have an overproduction of Aβ, show modifications in brain vasculature compared to the wild-type animals [12, 25]. APP23 AD model mice exhibit significant blood flow alterations correlated with structural modifications of blood vessels [51].

A study using three-dimensional architectural analysis [51], revealed significant changes to be accelerated only in the amyloid positive vessels [64]. Interestingly, brain homogenates taken from Aβ-overexpressing AD model mice, demonstrated an increase in the formation of new vessels in an *in vivo* angiogenesis assay [52]. This increase in vessels was blocked on exposure to a VEGF antagonist [52]. The vascular changes observed in these mice may be thought to be due to unrelated, 'off-target' effects of the APP mutation. However, the fact that the vascular changes observed in transgenic mice correlate well with vascular disturbances reported in human AD brains, it is safe to say that angiogenesis plays a crucial role in the establishment of AD pathology.

Post-mortem studies of human brains also show evidence of increased angiogenesis in the hippocampus, mid-frontal cortex, substantia nigra pars compacta, and locus coeruleus of AD brains compared to healthy individuals [43]. Further analysis found no correlation between the number of microglia (activation of apoptosis) and angiogenesis or microglia with vessel density, suggesting that it may be the presence of Aβ that is initiating angiogenesis (and not activation of apoptosis) and subsequently causing BBB dysfunction [66, 67].

It is seen that there are additional proteins at the BBB, which act to regulate brain Aβ levels and the disruption of which takes the brain towards up-regulated angiogenesis. The receptor for advanced glycation products (RAGE), a multi-ligand receptor, regulates the entry of peripheral Aβ to the brain [67–69]. Its expression is up-regulated by binding with ligands including Aβ and pro-inflammatory cytokine-like mediators [67]. This facilitates the entry of Aβ into the cerebral neurons, microglia and vasculature [69]. *In vitro* studies have also implicated RAGE in the vascular pathogenesis of AD, by suppressing the CBF, leading to hypoperfusion [67, 70].

3. Haemostatic mechanisms in relation to angiogenesis in AD

Maintenance of the fluidity of blood and limiting its loss upon blood vessel endothelium injury is a crucial physiological process known as haemostasis [71]. Haemostasis is possible due to the existence of a delicate balance between pro-coagulation and anti-coagulation along with numerous pathways and feedback loops [71, 72]. Haemostasis has three distinct phases—where the primary haemostasis is involved in adhering platelets to site of injury, forming a 'haemostatic or platelet plug' [71]; secondary haemostasis—which involves the activation of coagulation cascade, culminating in a fibrin clot; the last stage—which is fibrinolysis, or the dissolution of the clot [71]. Accompanied with vascular dysfunction, an altered haemostatic scenario is increasingly implicated in AD. Majority of the research, barring a few, support an association of pro-coagulation mechanism in AD. The proteins like transglutaminases are core components of the coagulation system that could be used as therapeutics to resolve the altered haemostasis in AD.

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3.1. The involvement of haemostatic factors in angiogenesis: transglutaminases (factor XIIIa and tTG)

Transglutaminases (TG) are a family of enzymes, which catalyse irreversible post-translational modifications of proteins [22, 73]. Yamada *et al.* put forward the suggestion that TG activity might contribute to the formation of protein aggregates in AD brain [21]. Though this idea is debated, tau proteins have been shown to be in support of this hypothesis by being an appropriate *in vitro* substrate of TGs [22]. Studies also show that transglutaminase-catalysed cross-links, co-localize with pathological lesions in AD brain. More recently, amyloid β-protein oligomerization and aggregation, at physiologic levels *in vitro*, have seen to be induced by the activity of TGs [22]. By these molecular mechanisms, TGs could contribute to AD symptoms and progression. Though the studies mentioned above support the involvement of TG in neurodegeneration, they fail to indicate whether aberrant TG activity, *per se*, directly determines the disease's progression [22].

Factor XIII (FXIII), a plasma TG, besides clot stabilization, plays an important role in wound healing and embryo implantation—a process that involves angiogenesis [74]. Haemostasis and angiogenesis are inter-related as can be seen by the haemostatic proteins assisting the spatial localization and stabilization of endothelial cells, which is succeeded by growth and repair of damaged vessels [74]. Post clot stabilization, the coagulation and fibrinolytic proteins regulate angiogenesis [74]. Thrombin-activated FXIII promotes endothelial cell migration, proliferation and inhibits apoptosis [74]. It is known to bind endothelial cell integrin $\alpha v\beta 3$. This binding enhances the integrin's interaction with VEGFR2, which then activates downstream, the Erk and Akt, thus augmenting cell proliferation [74]. This body of data suggests that there is an altered state of haemostasis that could contribute to AD pathology through angiogenesis.

4. Therapeutic modalities in treating pathogenic angiogenesis in AD

Angiogenesis, as stated by the studies mentioned in this chapter, can be viewed as that stage in AD pathology where all the different pathways (hypoperfusion, BBB dysfunction, inflammation) merge, leading to the AD pathology. Observations showing increased cerebrovascular permeability prior to the appearance of the hallmarks of AD, sprout a novel paradigm for integrating vascular remodelling (angiogenesis) with the pathophysiology of the disease. Targeting this integral step in the pathophysiology of AD and developing a novel therapeutic intervention using anti-angiogenic drugs can help to alleviate the global societal burden of AD.

4.1. Anti-angiogenics: small molecule tyrosine kinase inhibitors

Anti-angiogenics, including small molecule tyrosine kinase inhibitors have been tested and approved as anti-cancer therapeutics and have shown to maintain normal vascular [75–77]. Sunitinib is a broad spectrum tyrosine kinase inhibitor. This is known to inhibit the phosphorylation of multiple receptor tyrosine kinases and is a potent inhibitor of VEGF as well as platelet-derived growth factor (PDGF-β). Currently, it is in use for gastrointestinal stromal

tumours, renal cell cancer and pancreatic cancer. Sunitinib was shown to decrease the amyloid burden and reverse cognitive decline in AD model mice, suggesting that if we target angiogenesis, we can revert the increase in the accumulation of Aβ and abate the cognitive decline associated with AD [76].

4.2. Biologics and small molecule VEGFR inhibitors

We now know that VEGF is the prime and central component of pathological blood vessel formation. There are biologics and small molecules that specifically target the ligand or its receptor. This specific-targeted therapy could prove more efficient and less deleterious due to avoidance of unwanted 'off target' effects. A potential therapeutic is Bexarotene, a retinoid X receptor agonist, is shown to facilitate Aβ clearance via activation of apolipoprotein (APOE) expression and promoting microglial phagocytosis [78]. Bexarotene counteracts VEGF-mediated angiogenesis by decreasing blood vessel density and reversing cognitive deficits in AD mice [78].

These are examples of some of the therapeutic routes that could target angiogenesis; however, understanding the molecular mechanism behind angiogenesis causing eventual AD pathology is of utmost importance in order to look for safe and effective novel therapeutics for AD and other vascular diseases.

5. Concluding remarks

As the Western world ages, AD represents an ailment that will place a significant burden on all the aspects of society. This burden, primarily placed on family caregivers, has been estimated to cost billions in lost productivity and healthcare costs (both direct and indirect). Currently, there is a lack of understanding regarding the cause(s) of the disease that translates into a lack of viable treatments or cures. Over the years, limited progress has been made with regards to the clinical translation of the popular amyloid hypothesis for treating AD and hence new thinking towards AD pathogenesis is required. Vascular risk factors and neurovascular dysfunction associated with hypotension, hypertension, cholesterol levels, type II diabetes mellitus, smoking, oxidative stress and iron overload have been found to play integral roles in the pathogenesis of stroke and AD. Observations showing increased cerebrovascular permeability prior to the appearance of the hallmarks of AD, sprout a novel paradigm for integrating vascular remodelling (angiogenesis) with the pathophysiology of the disease. Taking this into account, research focused on understanding the molecular mechanism behind the pathophysiology of angiogenesis leading to AD pathology will mediate in developing novel therapeutic interventions targeting this pathological blood vessel formation help to alleviate the global societal burden of AD.

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