Review

A review of the complex roles of glial cells in Alzheimer's disease and potential glial-oriented therapeutic targets

Saif Shahriar Rahman Nirzhor[1, †], Rubayat Islam Khan[1, †, *], Sharmind Neelotpol[1]

[1]Department of Pharmacy, BRAC University, Dhaka, Bangladesh; rubayat.khan@bracu.ac.bd
*Correspondence: rubayat.khan@bracu.ac.bd; Tel.: +880-01731554050
† These authors contributed equally to this work.

Abstract: The pathogenesis of Alzheimer's disease (AD) is very complicated and not well-understood. As more and more studies are performed with regards to this disease, new insights are coming to light. Much of the research in AD so far has been very neuron-oriented however, recent studies suggest that certain glial cells i.e. microglia, astrocytes, oligodendrocytes, and NG2 glia are linked to the pathogenesis of AD and may offer several potential therapeutic targets in the long-standing battle against AD. Glial cells are responsible for maintaining homeostasis (i.e. concentration of ions and neurotransmitters) within the neuronal environment of the central nervous system (CNS) and are crucial to the integrity of neurons. This review explores the (1) role of glial cells in AD pathogenesis, (2) complex functionalities of the components involved and (3) potential therapeutic targets that it could eventuate leading to a better quality of life for AD patients.

Keywords: Glial Cells, Astrocytes, NG2 Glia, Microglia, Oligodendrocytes, Alzheimer's disease, Neurodegenerative disease. Aβ-peptides

1. Introduction

A debilitating neurological disorder, Alzheimer's disease is characterized by beta-amyloid (Aβ) and hyper-phosphorylated tau protein aggregation in the brain leading to a loss in cognitive ability and eventually dementia [1]. Since one of the greatest risk factors of AD is increasing age it is often manifest in many patient populations throughout the world. The approximate number of patients with AD in 2010 was 35 million and this number is projected to rise to 65 million in 2030. The prevalence of AD is almost double in human males compared to females and after the age of 85 the occurrence of AD is seen in almost 50% of the demographic [1]. AD can be classified into two different subgroups based on the age of onset of the disease. Familial AD (FAD) occurs at an early age of onset and sporadic AD (SAD) occurs at a much later age. FAD is a rare autosomal dominant genetic disorder that accounts for only a minor portion of AD cases. FAD symptoms appear in patients between the age of 30 and 50; and this specific disorder is characterized by mutations in amyloid precursor protein or presenilin 1 and 2 genes. SAD accounts for the majority of AD cases and the usual age of onset is observed to be 65 onwards. Even though the underlying mechanism of SAD still remains unknown, SAD has been linked to mutations in the Apolipoprotein E (ApoE) gene [2,3]. There are several methods of assessment available for AD patients, including tests of episodic memory and attention but a more definite diagnosis of AD can only be made post-mortem histological analysis. These analyses often reveal cerebral cortical atrophy, amyloid plaques, neurofibrillary tangles (NFTs) and vascular amyloidosis that collectively represent Aβ peptide deposits in the brain [4,5]. Much of the research on AD so far has been very neuron-oriented but in recent times, the interest in glial cells in this particular topic is markedly increasing

46   *1.1. Overview of the role of glial cells in AD:*

47   Looking at the nervous system from a broad perspective, it is built using two types of cells i.e.
48   neurons and glial cells. Glial cells are the majority in terms of numbers even though they occupy
49   similar amount of space in the nervous tissue. The glial cells involved in the nervous system are:
50   oligodendrocytes, polydendrocytes (NG2 glia), astrocytes, Schwann cells, satellite cells, microglia,
51   ependymal cells and enteric glial cells. These glial cells function to maintain homeostasis (i.e.
52   concentration of ions and neurotransmitters) within the neuronal environment, aid in the formation
53   of myelin sheaths around the axons in the nervous system responsible for the cell-to-cell signaling
54   and maintain the function of synapses [6]. When this homeostasis is disrupted the progression of
55   neurodegenerative diseases such as AD may be accelerated [6]. Researchers in neuroscience
56   disciplines have put in considerable amount of effort and managed to limn the importance of glial
57   cells AD research through the in vivo studies in various animal models.

58   *1.2. In vivo models used for the study of AD:*

59   Animal models, especially murine models have been widely used in the studies regarding AD
60   pathogenesis. SAD is the more common form of AD that is more complicated to study compared to
61   FAD. However, studying FAD is somewhat more feasible to observe in murine models. If there is an
62   underlying assumption that the two of types of AD have similar genetic origin, then AD may be
63   studied more practically using these models. Some murine models that have been pivotal in
64   identifying the neuropathology of AD [7–16]. studies on specific types of glial cells have been done
65   on specific mouse models. In order to piece together the information accurately the murine models
66   and their studied alterations in glial cells and neurons are depicted in Table 1. These are just a few
67   examples and a comprehensive guide to these murine models and relevant findings can be found in
68   the Alzforum website (https://www.alzforum.org/research-models) where a database was created to
69   aid in AD research.

70   **Table 1.** Some well-studied murine models for AD and observed alterations in specific types of glial
71   cells

Murine Model	Observed loss of neurons	Observed alteration in microglia	Observed alteration in astrocytes	Observed alteration in oligodendrocytes	Observed alteration in NG2 glia
PDAPP-J20	✓	✓	✓	✗	✗
Tg2576	✗	✓	✓	✗	✗
APP23	✓	✓	✓	✗	✓
APP NL-F	✓	✗	✓	✗	✗
APPswePS1dE9	✗	✗	✓	✗	✓
5xFAD	✓	✗	✓	✗	✗
3xTg-AD	✓	✓	✓	✓	✗

APP/PS1	✓	✓	✓	✗	✓
PS1mutK	✓	✗	✗	✓	✗

72   ✓ = alterations have been studied and observed

73   ✗ = alterations have not yet been studied or no observed alterations were reported

74   These models are indeed helpful in terms of looking at the pathogenesis of AD but more
75   importantly these may give some insight into the potential therapeutic targets that may exist.
76   However, it is worthwhile to notice that these models do not accurately mimic AD and the many
77   complexities it creates. Moreover, there could be several problems related to the interpretation of
78   these kinds of data from animal models to humans that may obfuscate the lucidity of the observed
79   phenomena. For example, in some of these models, fragments of APP, such as intracellular
80   cytoplasmic domain (AICD) or α-secretase cleaved secreted APP (α-APPα) may also show
81   overexpression along with APP. These fragments may exhibit some functions in the host that may be
82   observable clinically. For example, in Tg2576 mice (shown in Table 1), the overexpressed α-APPα
83   upregulates insulin like growth factor-2 (IGF-2) and protein transthyretin (TTR) that may lead to
84   some neuroprotective properties for the mice. This may be one of the reasons why these mice often
85   do not show a significant amount of neuronal loss [17]. Another reason the interpretation may be
86   hard is that wild-type mice that overexpress APP may show cognitive decline even without Aβ
87   deposits being formed in the brain [18]. The interpretation become even more nebulous for a
88   modeled organism when, due to alternative splicing, the transgene mRNA of APP might be altered
89   and the composition may differ from endogenous APP; this becomes even less manageable when the
90   variability across different organisms is taken into account. This variability is an issue since the
91   models are usually selected by looking at the phenotype similarity between the model and human
92   [19,20]. Regardless of the challenges, murine models have been a useful tool in identifying the roles
93   of various glial cells in the pathogenesis of AD and this review will focus on these individual cell
94   types and their potential therapeutic applications separately.

95   **2. Microglia**

96   Microglia is an essential part of the substructure that is responsible for maintaining the
97   homeostasis within the neuronal environment. Microglia are ubiquitous in the central nervous
98   system (CNS) and more senescent they become they become increasingly less able to perform their
99   cellular functions [21]. It has been observed that the physiological decline in microglia in proportion
100   to the age of the brain in humans is similar to the decline in function in AD. However, these changes
101   are more pronounced in AD patients. Microglia pathogenesis is accompanied by the release of
102   neurotrophins or inflammatory cytokines which may have detrimental or supportive effect on
103   neurons [22–24]. In murine animal models, it has been observed that morphological changes in
104   microglia occur at a higher degree in aged mice compared to their young counterparts. Usually
105   microglia morphology can switch between an "active" state and a "resting" (ramified) state. In aged
106   mice, these cells become less ramified and more "active", cause neuronal hypertrophy and become
107   less active in the CNS; more specifically in the corpus callosum, striatum, substantia nigra, dentate
108   gyrus, cerebellar nuclei, inferior cerebellar penducle and the molecular layer of the cerebellar cortex
109   [25,26]. Mouse models that overexpress mutated version of human APP show that these
110   morphological changes in the microglia appear around six months' time and are accompanied by a
111   loss of activity in the brain parenchyma [27]. In PDAPP-JO mice these changes start manifesting as
112   early as 3 months' time [ibid]. In the healthy aged brain, microglia are the main source of
113   pro-inlflammatory cytokines such as TNFα, IL1β, IL1α, IL6, nitric oxide etc. [28–31]. During AD
114   pathogenesis, they also release IL-4, IL-10, IL-13 and transforming growth factor (TGF)-β1. Studies
115   done on murine models indicate that the increased production of these cytokines may damage
116   neurons in their vicinity especially since a decrease in TGF-β1 was observed in models that

117 underwent Aβ clearance by phagocytosis during AD pathology [31]. Since the release of these
118 cytokines and phagocytosis are the main functions of activated microglia, researchers have also
119 looked into Ca^{2+} signaling that is responsible for their regulation. A recent study in APPPS1 mice as
120 well as in AD patients revealed that the intracellular concentrations of Ca^{2+} are noticeably increased
121 in the activated microglia around Aβ plaques tending towards to the conclusion that the increase in
122 Ca^{2+} signaling is associated with neurodegeneration in AD patients [32–34].

123   Even though the role of microglia seems to be very relevant to the conversation, the problem of
124 interpreting the results of these models accurately to humans still remains a challenge however.
125 Studies done on human Alzheimer's disease tissue (hAD) suggest that Aβ deposits do not directly
126 trigger microglial activation, rather their progressive degeneration and subsequent loss of
127 neuroprotection may contribute towards to the onset of AD cases [24,35]. These findings contradict
128 the mouse model inferences that microglial activation and neuro-inflammation contributes towards
129 AD phenotype. Another issue that researchers are having to constantly go back and forth on is in the
130 case of microglia proliferation. Some studies show that the cellular proliferation may contribute
131 towards AD pathogenesis while others argue against it. For example, it was recently identified when
132 hippocampus of 3xTg-AD mice were compared with human hippocampus of control subjects in
133 which the microglial proliferation observed in the mice were not seen in the human subjects [36]. In
134 contrast, another study revealed that there was an increased number of microglia present in the
135 temporal cortex of human AD patients compared to their non-demented control groups [37]. To date
136 the best consensus seems to be that that the phenotypic changes in the microglia are of more
137 importance compared to the increased proliferation rates in AD patients.

138   Evidence indicate that the morphological changes of microglia may be reversed by Aβ
139 vaccination which may reduce Aβ deposits overall [27]. In addition to morphology, genetic studies
140 have revealed that variations in genes that responsible for encoding microglial proteins are strongly
141 related to AD pathogenesis. In a recent study with APPSwe/PS1dE9 mice, it was observed that the
142 gene TREM2 (Triggering Receptor Expressed on Myeloid Cells) is upregulated in microglia and
143 becomes more pronounced as AD progresses [38]. Even though originally TREM2 was identified as
144 a risk gene for AD, this study showed that TREM2 may indeed facilitate Aβ phagocytosis and in turn
145 improve patient cognitive functions by slowing down AD progression by increasing
146 neuroprotection. Therefore TREM2 may eventually become a potential therapeutic target in terms of
147 glial cell oriented therapy for AD.

148 **3. Astrocytes**

149   In the human brain, the circuitry is formed by neuronal networks which are embedded in
150 astroglial syncytia. Astrocytes have numerous functions which include assisting in neurogenesis,
151 maintaining overall homeostatic in the brain, structuring the grey matter etc. In the early stages of
152 neurodegenerative diseases or brain injuries, astrocytes often atrophy and in the later stages, they
153 become activated and may cause neuroinflammation that contribute towards neurodegeneration
154 and cell death [39]. Studies on hAD tissues and APPswePS1dE9 mice have confirmed that astrocytes
155 in the brain of AD patients upregulate immune response through gene activation and contribute
156 towards chronic inflammation and associated oxidative stress that may cause irrevocable cell
157 damage and ultimate cell death [40,41]. Astrocytes most abundant non-neuronal cells in the CNS
158 and they modulate activity of synapses and moderate local blood flow through Ca^{2+}-dependent cell
159 signaling [42]. During progression of AD, astrocytes go through noticeable morphological changes.
160 These phenomena are observed in studies of brain tissue of 3xTg-AD mice where astrocytes in the
161 entorhinal cortex show marked atrophy at the early stages i.e. around 1 month well ahead of
162 detectable Aβ plaque formation [43]. In the same mice, after considerable AD progression and the
163 development of extracellular plaques, the atrophy is still observable even when the astrocytes are
164 not in contact with the plaques [44]. However, in terms of number, there is no marked differences in
165 the rate of proliferation or degeneration when AD human brain tissue was compared to healthy

166 control group tissue via post-mortem analysis [45–47]. The formation of Aβ plaques in AD patients
167 often results from a lack of Aβ clearance [48]. Astrocytes are responsible for enlisting several
168 enzymes such as neprilysin (NEP), angiotensin-converting enzyme (ACE), endothelin converting
169 enzyme (ECE), insulin degrading enzyme (IDE) and matrix metalloproteinases that degrade Aβ
170 plaques [49–51].

171   Researchers have posited a possible explanation of the roles of astrocytes in the early stages of
172 AD by inferring that when astrocytes detect Aβ released by affected neurons, they withdraw their
173 support from all the neurons in the vicinity creating a feed forward loop that results in the
174 acceleration of Aβ plaque formation [52]. Studies done on hAD samples show similarly that during
175 AD progression, astrocytes are responsible for accumulating Aβ and when overloaded, form their
176 own Aβ plaques when they undergo lysis [47]. Astrocytes may upregulate the protein known as
177 glial fibrillary acidic protein (GFAP), which modulates immune response in the CNS, usually to
178 neurodegeneration or traumatic brain injury [53,54] Studies in APP/PS1 mice have shown that the
179 deletion of GFAP which inhibits astrogliosis showed a marked increase in Aβ plaque formation
180 thereby confirming the role of astrocytes in Aβ degradation [55]. However, astrogliosis may not
181 always be beneficial in the sense that sustained proliferation of astrocytes during AD progression
182 has been correlated with an increase of NFTs in human brain tissue [56].

183 *3.1. Astrocytic Ca^{2+} homeostasis in AD:*

184   A significant amount of evidence suggests that Ca^{2+} homeostasis is often altered by Aβ. Murine
185 model studies have revealed that astrocytes in Aβ overloaded tissue have increased concentration of
186 Ca^{2+} [57]. In mouse models, these abnormal Ca^{2+} concentrations have been shown to be associated
187 with the increased activation of P2Y1 receptors and transient receptor potential channel 4 [58,59]. In
188 3xTg-AD mice, Ca^{2+} release is observed from the endoplasmic reticulum (ER) of astrocytes by Aβ
189 following stress on the ER [60]. Increased concentration of Ca^{2+} activates phosphatase calcineurin
190 (CaN) and downstream targets for example, nuclear factor kappa-light-chain-enhancer of activated
191 B cells (NF-κB) and nuclear factor of activated B cells (NFAT). In Tg2576 mice, NFAT or CaN
192 inhibition decreases neuronal degeneration induced by Aβ [ibid]. Also evidence from studies in rat
193 primary astrocytes suggest that CaN activation may contribute towards Ca^{2+} overload [61,62].

194 *3.2. Astrocytic function and neurotransmitters in AD:*

195   At the synapse, the clearance of excess glutamate, its conversion to glutamine and the
196 re-synthesis of glutamate is one of the primary astrocytic functions. Glutamate aspartate transporter
197 (GLAST), glutamate transporter – 1 (GLT-1) and glutamine synthase (GS) is expressed by these cells
198 for the purpose of maintaining this glutamate homeostasis. In 3xTg-AD mice and hAD samples, GS
199 expression is attenuated by the progressive formation of Aβ [63,64]. In the hippocampus and cortex
200 of AD patients, there is a noticeable decrease in GLT-1 expression which is further evidence of this
201 disruption in glutamate homeostasis [65]. This disruption may be play a role in glutamatergic
202 transmission and neuronal damage in AD. Moreover, studies on the cerebellum of healthy murine
203 models show that astrocytes release GABA through bestrophin channel (Best 1) which inhibit
204 synaptic function; GABA (γ-aminobutyric acid) is a primary neurotransmitter in the mammalian
205 CNS [65]. From the hippocampus of APP/PS1 mice, it has been observed that there is an
206 enhancement of this Best 1-mediated release of GABA, in the vicinity of Aβ plaques, from active
207 astrocytes indicating that Aβ plaques may play a role in increased astrocytic GABA synthesis [ibid].
208 Furthermore, studies on hAD samples show that there is an increased expression of
209 monoaminooxidase B, which is a GABA-synthesizing enzyme in astrocytes, and the total number of
210 GABA positive astrocytes as a whole further clarifying the role of GABA positive astrocytes in AD
211 [66]. All of these findings taken together show strong correlation of astrocytes in the involvement of
212 AD progression.

213   Studies done on APP/PS1 mice have shown that the inhibition of CaN/NFAT pathway in
214   astrocytes slows down astrogliosis and consequently improves cognitive functions [67]. In 2012,
215   Furman et al. showed that using adeno-associated virus (AAV) vectors that contained
216   astrocyte-specific Gfa2 promoter they were able to target the hippocampal astrocytes in APP/PS1
217   mice. The vectors stimulated the expression of VIVIT, which is a peptide that interferes with the
218   calcineurin/NFAT pathway leading to reduced astrocytic activation. When this treatment was ran
219   for several months, the mice showed diminished glial activation, lower Aβ levels and improvements
220   in synaptic and cognitive function. These results are promising and warrant further exploration of
221   novel astrocyte-based therapies for AD.

222   **4. Oliogodendrocytes**

223   Another important class of glial cells that have been part of AD research for a significant period
224   of time is oligodendrocytes. These cells are responsible for providing insulation and support to the
225   neuronal axons in the CNS required for the fast action potential propagation. Evidence suggests that
226   structural and spatial organization of myelin lipid bilayers have a strong connection with the
227   pathogenesis of AD [68,69]. As with microglia and astrocytes, oligodendrocytes have also shown to
228   exhibit specific morphological changes during AD progression. In PDAPP mice of age 15 months as
229   well as hAD samples, researchers have used imaging studies and X-ray diffraction to show that near
230   the Aβ plaques, there is noticeable deterioration in myelin integrity and axonal destruction [68,70–
231   73]. Electron microscopy and myelin staining revealed that 3xTg-AD mice of age 2-6 months
232   compared to control groups exhibit myelin sheath alterations and impairment of axonal morphology
233   possibly due to a loss of oligodendrocytes [74,75]. In terms of numbers however, most studies on
234   mouse models and hAD samples have revealed that while the myelin integrity is compromised in
235   most cases, the overall amount of myelin largely remains unchanged [74,76,77]. When the impact of
236   Aβ is studied on oligodendrocytes, it has been demonstrated through TUNEL staining and MTT
237   cytotoxicity assay that the treatment with Aβ usually results in the breakdown of cell processes,
238   shrunken cell bodies and DNA damage in these cells [78]. Aβ treatment in oligodendrocytes has also
239   been seen to induce release of cytosolic cytochrome C and increased binding activity of AP-1 and
240   NF-κ suggesting that oxidative stress may be, in part, responsible for cell death [78]. This cytotoxic
241   effect of Aβ on oligodendrocytes was prevented with the introduction of LPS and INF-γ, which are
242   pro-inflammatory in nature and also when the cells were co-cultured with astrocytes [79]. However,
243   morphological analysis still showed persistent damage to the oligodendrocytes.

244   More recently, Aβ treatment on oligodendrocytes have been showed to increase in the levels of
245   caspase-3. The accumulation of caspase-3 leads hindrance of the branching and elongation process
246   of oligodendrocytes by blocking of the local re-organization of microtubules [80]. Park et al.
247   demonstrated that in PS1mutK1 mice, cultured oligodendrocytes exhibit higher levels of Ca^{2+}
248   concentrations compared to control groups which may be a critical factor in ultimate cell death [81].
249   Another recent study reported that AD progression causes an increase in the DNA damage by
250   upregulating the growth arrest DNA damage protein (GADD) [82]. Taken together, the changes in
251   functionality and morphology of oligodendrocytes resulting from compromised myelin integrity
252   indicate that oligodendrocytes are also victims during AD progression and eventually contribute
253   towards cognitive dysfunction such as impaired learning ability. However the extent of involvement
254   of these cells largely remains unknown.

255   *4.1. Antioxidants that may be used to treat AD:*

256   Oxidative stress i.e. lipid peroxidation and protein oxidation, plays an important role in AD
257   with oligodendrocytes and neurons being more susceptible compared to microglia or astrocytes.
258   Neurons are dependent on astrocytes for the supply of glutathione (GSH) precursors; the
259   Aβ-mediated Ca^{2+} disruption in astrocytes has been shown to result in the death of these neurons.
260   Oligodendrocytes also maintain low concentrations of GSH which in conjunction with higher iron

261 concentrations may attenuate the ability of these cells to scavenge for reactive oxygen species (ROS).
262 Therefore, a reasonable link is formed between Aβ-mediated and antioxidant capacity of the CNS.
263 N-acetylcystein has been shown to prevent Aβ-induced cellular death in oligodendrocytes [78]
264 whereas trolox, which is a vitamin E analog, has been shown to reduces cell death in astrocytes and
265 neurons [58]. In addition, curcumin has been shown to increase concentrations of GSH by increasing
266 the activity of glutamate-cystein ligase (a GSH synthesizing enzyme) potentially offering up higher
267 neuroprotection from AD [83].

268 **5. NG2-glia**

269 Polydendrocytes or oligodendrocyte precursor cells (OPCs) or NG2-glia are the latest discovery
270 in glial cell types but their role in the pathogenesis in AD are already of major interest [84]. When
271 glial progenitor cells (GPCs), largely composed of NG2-glia, were studied in 12 and 24 month old
272 APP23 mice, neuroblast percentage in the GPC progeny were markedly reduced compared to
273 control mice [85]. An explanation posited for this phenomena in GPCs was that there were reduced
274 levels of Mash1, Ngn2 and NeuroD1. In hAD sample, similar observations were seen compared to
275 human control subjects. In addition, the GPC progeny of both models showed reduced levels of
276 β-catenin while glycogen synthase kinase (GSK-3β), an enzyme that phosphorylates β-catenin) and
277 phosphorylated β-catenin levels were increased. In APP23 mice, the expression levels of GSK-3β was
278 reduced accompanied by an increase in β-catenin and Ngn2 when treated with GSK-3β-siRNA. In
279 combination with previous studies, this was evidence of the fact that Aβ activates GSK-3β resulting
280 in the increased phosphorylation of β-catenin resulting in β-catenin degradation and the inhibition
281 of the Wnt signaling pathway [86]. This inactivation of the Wnt signaling pathway through Aβ
282 toxicity leads to the inhibition of the differentiation of NG2-glia [87]. However, a recent studies also
283 suggest that Aβ does not have a direct impact on the survival rate of oligodendrocytes after the
284 induction of NG2-glia in vitro [80]. A comprehensive investigation by Nielsen et al. of NG2-glia and
285 human AD patients recently revealed that individuals with an overexpression of Aβ showed
286 reduced NG2 immunoreactivity, dense cellular bodies and reduced levels in cell lysates even though
287 cell viability remained largely unchanged. Furthermore, the group reported reduced levels of NG2
288 in cerebrospinal fluid (CSF) of AD patient even though there was no link with cognitive decline in
289 those cases [88]. In contrast, another group reported that the number of NG2-glia increased in 12-15
290 month old APPswe/PS1dE9 mice compared to age-matched control groups. Indeed due to the lack
291 of knowledge on the issue, the debate on the exact involvement of NG2 glia remains largely
292 uncertain but this avenue of research may be worthy of pursuit as more and more studies are
293 performed.

294 *5.1. Stimulation of Wnt pathway in the treatment of AD:*

295 Since Aβ action increases the expression levels of GSK-3β and phosphorylated β-catenin,
296 stimulation of the Wnt/β-catenin pathway may be a potential way to mitigate AD pathology [87]. In
297 vitro and in vivo studies, particularly on those on 3xTg-AD mice, have shown that GSK-3β inhibitor
298 TWS119 has mitigated impaired myelination of neurons [89]. Similar stimulation of this signaling
299 pathway may have a role in reducing glutamate excitotoxicity in astrocytes as well. In APP/PS1dE9
300 mice, it was seen that stimulation by pyrrolidine dithiocarbamate (PDTC) increased GLT-1 levels as
301 well as reduced the extent of tau protein phosphorylation which is another major identified
302 component along with Aβ buildup [90]. Furthermore, a recent study on APPswePS1dE9 mice
303 showed that rosiglitazone or lithium caused similar stimulation and reduced astrogliosis, levels of
304 activated microglia and Aβ plaque load [91]. Stimulation of this pathway does come at a cost
305 however since studies on hAD samples showed that the increased levels of β-catenin and
306 consequently the increased level of activated microglia leads to an increase in AD
307 neuroinflammation which counteracts the enhanced Aβ clearance through phargocytosis by the
308 same microglia [92].

309   **6. Other potential therapeutic targets of interest**

310   There are other approaches that are being investigated as well with regards to glial-oriented AD
311   therapy. For example, neural stem cells (NSCs) engraftment holds much promise in AD since NSCs
312   are responsible for producing various beneficial factors such as neurotrophic factors that promote
313   the regeneration of the CNS as well as migrating to sites of injury and differentiating into neural
314   cells. Studies on 3xTg-AD mice show that the engraftment increased the number of
315   oligodendrocytes and astrocytes as well as increased levels of brain derived neurotrophic factor
316   (BDNF) but did not alter Aβ deposition or tau protein phosphorylation [93].   Another interesting
317   line of research has been perused through the production of Cortical GABAergic interneurons from
318   embryonic medial ganglionic eminence (MGE) cells [94,95]. Immature progenitor cortical
319   interneurons are produced, transported and distributed all through the hippocampus and cortex in
320   the brain. Studies have shown that this particular structure can in fact be dissected from rodent
321   embryos and transplanted to adult animals. The transplant recipients showed promise in several
322   neurodegenerative disorders and these cells may become an attractive target for AD in the near
323   future [98-109]. Furthermore, another group of researchers showed that in 5xFAD mice, the
324   increased expression of BDNF can be induced by sodium phenylbutyrate and can repair synapses
325   improving cognitive function [108]. In 3xTg-AD mice, intentional glial cell derived neurotrophic
326   factor (GDNF) overexpression also showed conservation of memory and learning capability in vivo
327   as well as decreased oxidative stress and cellular death in vitro [109]. A schematic diagram of the
328   glial-oriented potential therapeutic agents are outlined in Table 2.

329   **Table 2.** A summary of the agents that may have therapeutic applications in AD

Agent	Mechanism of action
Trolox	Reduced death of neurons and astrocytes [58]
N-acetylcystein	Reduced death of oligodendrocytes [78]
Curcumin	Increased concentrations of GSH in neurons and astrocytes [83]
TWS119	Improved myelination [89]
Pyrrolidine dithiocarbamate (PDTC)	Increased levels of GLT-1 [90]
Lithium/rosiglitazone	Reduced AB load [91]
NSCs (transplantation)	Improved cognitive functions [93]
Sodium phenylbutyrate	Improved cognitive functions [108]

330   **7. Conclusions**

331   The attempt to understand AD all of its complexities yielded mixed results so fat but as more
332   data becomes available, more complex and exhaustive approaches can be identified that will
333   eventuate a more concrete understanding in the near-future. At its core, the understanding of the
334   etiology of AD still remains an issue. It is very difficult to pinpoint the exact origin of AD and the key
335   players involved. As of yet, no concrete therapy exists that can reverse AD progression and

336   researchers may have to adapt complex approaches in order to treat AD. Many treatment options
337   have been investigated but in this review we only outlined the glial-oriented strategies that showed
338   promise. In order to get a better understanding, a more global view of AD needs to be assimilated. A
339   plethora of data exists for AD in terms of neuron oriented research; together with glial-oriented
340   approaches, small pieces of information are coming out of hiding one-by-one. All of this can be taken
341   together to piece together a more macroscopic view of AD that may answer some long standing
342   questions that still persist. There is still long ways to go in this line of research but the glial-oriented
343   research into AD may open new doors that can help a significant amount of AD patients around the
344   world.

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