Commentary

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The Effects of Amyloid Beta Aggregation on Neuronal Transcription: A Commentary

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Description

The World Health Organization has estimated that there are 50 million people worldwide who suffer from dementia as of 2017, with estimates that that number will triple by 2050 [1]. By some estimates two thirds of these cases can be directly attributed to Alzheimer's Disease (AD) [2].

As such there is a growing need for the development of platforms for the treatment and diagnosis of this disorder. One of the largest obstacles currently preventing treatment and diagnosis is that the current understanding of AD is limited. AD is well known for its behavioural phenotype, however knowing its cellular pathology, which is primarily based on the presence of Amyloid Beta (Aβ) in various aggregation states, is crucial for the development of research efforts against the disorder [3].

The most notable of these aggregation states are the oligomeric and fibril forms of Aβ [4]. Despite the understanding that this protein is the defining characteristic of the disorder, there is still debate as to whether Aβ is the cause of the deleterious effects or whether it is a symptom of a further underlying cause of the disorder. As such, the presented research aimed to determine what the downstream effects of Aβ are on neurons and by doing so illustrate what deleterious effects Aβ causes. To accomplish this goal this paper quantified the transcriptomic profile of neuronal cells exposed to these aggregation states of Aβ. It is hoped that through doing so, a more complete understanding of AD can be garnered, and that this information can be used identify potential therapeutic genetic targets. The primary findings of this paper illustrate the significant effects of Aβ on genes associated with metabolism as well as the dramatically increased effects of oligomeric Aβ relative to fibril Aβ with respect to the overall changes in gene expression. The presented results also support the further examination of the role of GTPases in the negative effects of Aβ. Changes in metabolism, specifically in glucose metabolism and lipid metabolism illustrate an interesting link between Aβ and several other theories surrounding AD. Changes in glucose metabolism specifically as it pertains to insulin-dependencies has long been documented in AD, and has led some researchers to use the term "type 3 diabetes" to describe AD [5].

The presented research then suggests that changes in glucose metabolism and utilization may be a direct result of Aβ deposits, and as such strengthens the hypothesis that neuronal damage due to decrease energy consolidation is directly caused by Aβ rather than Aβ deposits being an effect of said changes in glucose utilization. An interesting finding in the presented research is the changes of glutathione metabolism. Specifically, it supplies a potential route for a cause of the oxidative damage associated with AD [6].

The presented results show that Aβ can dysregulate glutathione metabolism. Glutathione is a cellular antioxidant and therefore alterations in the genes associated with its metabolism can lead to decreases in the reduction of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) [7]. The hypothesis of Aβ causing oxidative stress through glutathione is also supported by the changes in Rho-GTPase signalling. It has been noted that the replenishing of intracellular glutathione stores prevents Rac1-mediated down regulation of RhoA-GTP [7]. This is significant as RhoA has a tentative role in decreasing RNS, and as such the combination of changes in glutathione metabolism and Rho-GTPase suggest that RNS may be an important avenue of exploration when considering oxidative stress in AD [7].

Some of the earliest theories of AD have been linked to alterations in cellular communication [8]. In fact, many of the drugs currently available for treatment are based on changes in the amount acetylcholine found in AD patients due to changes in choline acetyltransferase [9,10]. In more recent years, glutamate signalling has also been implicated in AD, thereby solidifying the decrease in intracellular communication in the etiology of AD. Specifically the relation of the NMDA glutamate receptor to AD is strongly supported by the positive impact of the NMDA receptor antagonist memantine in ameliorating some of the symptoms of AD [11].

Considering the presented research illustrates alterations in both membrane trafficking and signalling molecules, the downstream effects of Aβ may offer a potential explanation for the disruption of the proper function of these neurotransmitter systems. The presented research shows that Rho-GTPases are disproportionally affected by Aβ and considering the role of these proteins in the formation and function of the synapse, this also suggests that neurotransmission deficits can be attributed directly to Aβ rather than Aβ plaques being caused by changes in neurotransmission [12]. This is especially notable as it seems that Rho-GTPases are vital for longterm potentiation linking their disruption to the most well-known side effect of AD, namely decreased memory consolidation [13]. As such, the presented research strongly supports the alterations of Aβ as being the causative agent of the negative effects of AD and provides some potential routes for how Aβ deals damage to the cells.

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