EBioMedicine 39 (2019) 17–18

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

Moving towards a more realistic concept of what constitutes Alzheimer's disease

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The results presented in the article of *EBioMedicine* by Medawar et al. [1] highlight the complexity of the underlying mechanisms that drive Alzheimer's disease (AD). The old concept that the disease is primarily driven by beta-amyloid aggregation has not been supported by data from clinical trials which successfully lowered the levels of amyloid in the brains of patients but failed to stop disease progression [2,3]. The results presented in this paper draw a much more complex picture. In the TASTPM transgenic mouse model which expresses the Swedish mutation of the APP gene and the M146 L mutation of the presenilin-1 gene [4], amyloid plaques are not observed until later in the development, while an inflammation response is already ongoing as shown by the proliferating microglia. Importantly, there is an initial improvement in the neurophysiological functions of transgenic mice that express the mutated human APP gene. At 2 months of age, LTP was enhanced in the hippocampal area CA1 in transgenic mice compared to wild type animals. At 8 months, the transgenic mice performed better in the T-maze task, a difference that disappeared as mice grew older. Similar results have been reported previously in APP-overexpressing mice which displayed improved learning and LTP in the hippocampus [5]. This improvement is a reminder that APP is a membrane standing receptor that plays important roles in cell growth and repair [5]. Only as the increased expression of APP continues, and amyloid starts to accumulate, the positive effect of APP overexpression is outweighed by the detrimental effect of mutated amyloid building up in the brain. From 4 months of age, LTP was impaired in transgenic TASTPM mice. The mechanism that starts to reverse the advantage of APP expression appears to be the activation of a chronic inflammation response. Microglia started to proliferate early and then became activated at around 8 months of age: after that, the learning improvement disappeared. As the mice grew older, the continuing inflammation response took its toll, and synaptic plasticity in the hippocampus was seriously impaired in 12 months old mice. However, when looking at the learning task results, there was no difference between groups.

The results of this study are a timely reminder that AD is a complex syndrome that goes through several stages and involve numerous factors. The hypothesis that AD is only caused by the build-up of amyloid has to be discarded as being too simplistic [6,7]. The image that emerges is that AD is an ongoing process where beta-amyloid is only one parameter of many. The initiation of chronic inflammation and the corresponding release of pro-inflammatory cytokines, which impair synaptic activity, cell repair and cell metabolism while increasing levels of oxidative stress constitute important factors [8–10]. As simply removing amyloid from the brains of patients had shown little effects, we have to address numerous other factors such as the inflammation response and the effects of pro-inflammatory cytokines on cell metabolism and repair if we are to make a visible impact on disease progression, as well as the resulting loss in growth factor signaling [11,12]. Growth factor signaling desensitizes in the brains of AD patients and reduce cell growth and repair, energy utilization, synaptic activity and autophagy [13–16].

A multi-target approach that lowers amyloid levels, reduces the inflammation response and reverses the detrimental effects of pro-inflammatory cytokines by boosting activity of their counterplayers, the growth factors, offers a lot more promise to be efficient in stopping disease progression in AD.

Author's contribution

The commentary has been written by C. Hölscher.

Declaration of interests

The author declares no conflict of interest.

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DOI of original article: https://doi.org/10.1016/j.ebiom.2018.12.006.
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https://doi.org/10.1016/j.ebiom.2018.12.030

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