Reestablishing microglia function: good news for Alzheimer's therapy?

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Alzheimer's disease (AD) is the most common form of age-related neurodegenerative disease resulting in dementia. The current notion is that AD is based on a pathological plaque-forming accumulation of amyloid- β (A β) peptides that originate from a disturbed balance between production and removal of A β peptides. Loss of A β uptake capacity by brain microglia is linked to A β plaque formation and AD onset. In this issue of *The EMBO Journal*, Daria and colleagues show that this microglia dysfunction is reversible and that existing A β plaques can be cleared, suggesting that restoring microglia function may be vital for treating AD.

See also: **A Daria *et al*** (March 2017)

It is widely accepted that an imbalanced production versus clearance of A β peptides is the pathological origin of AD. Recent genome-wide association studies have revealed various AD risk alleles that belong to innate immunity and that are functionally linked to phagocytosis (Hardy *et al*, 2014). Impaired uptake of A β peptides and microglia dysfunction was described in mouse models of AD (Hickman *et al*, 2008; Krabbe *et al*, 2013; Orre *et al*, 2014; Hellwig *et al*, 2015). In humans, microglia senescence and presumably dysfunction precede AD pathology (Streit *et al*, 2014) and decreased A β clearance rather than increased production was reported in sporadic AD patients (Mawuenyega *et al*, 2010). The loss of microglia A β uptake capacity may explain why depletion of microglia in mice did not change A β plaque

load in mouse models of AD (Grathwohl *et al*, 2009). Instead, microglia in AD may acquire a pro-inflammatory phenotype contributing to disease progression (Heneka *et al*, 2013). Microglia function in AD thus is complex, and it is important to understand whether their protective A β uptake capacity to limit plaque formation can be restored. This question was addressed in a recent paper by Daria *et al* (2017).

To address this question, Daria and colleagues developed a new *ex vivo* system based on the membrane interface method for culturing brain cells similar to a system used recently to investigate A β plaque formation in culture (Hellwig *et al*, 2015). Instead of culturing slices from one animal only, Daria *et al* (2017) co-cultured slices from 20-month APPPS1 animals together with slices from neonate wild-type animals. They observed that A β plaques present in the APPPS1 slices became smaller in the co-culture situation. More specifically, Daria and colleagues found that the halo of A β plaques was in this case removed by CD68-positive microglia by phagocytosis. Depletion of microglia by clodronate treatment in either young or old slices before co-culturing prevented this effect, suggesting that microglia in both slice compartments were required. To study which microglia population (old or young) was responsible for the phagocytosis of the A β halo, Daria and colleagues used slices from neonate heterozygous CX3CR1-GFP animals. As green microglia from neonate CX3CR1-GFP animals never invaded the parenchyma of old APPPS1 slices, it was concluded that the A β halo was removed by old microglia present in the APPPS1 tissue. A series of

experiments with supernatants revealed that microglia in neonate slices release a factor that stimulates the A β plaque phagocytosis of old microglia, and this was at least partly due to GM-CSF, a known proliferative growth factor for microglia. Indeed, prevention of cell proliferation by AraC treatment also prevented the removal of A β plaque halo by the old microglia. These data elegantly indicate that plaque removal capacity of old microglia can be restored.

Do these data provide hope for AD therapy? Is the removal of A β plaques beneficial for AD patients? One principal idea to fight AD is the use of anti-A β antibodies as therapeutic agents. Recent promising findings suggest that this strategy indeed might be successful, as A β plaque reduction was correlated with slower clinical decline in AD patients (Sevigny *et al*, 2016). With respect to the data presented by Daria and colleagues, it is interesting to point out that, although the mechanism is not fully understood, anti-A β antibodies stimulate microglia to remove A β plaques (Sevigny *et al*, 2016). Recent and rather surprising data suggest that microglia A β uptake capacity can also be induced by 40-Hz gamma frequency stimulation (Iaccarino *et al*, 2016). Thus, there are various ways to enhance A β uptake capacity of microglia. Whether or not GM-CSF or 40-Hz stimulation may further enhance efficacy of antibody therapy in AD remains to be established. These recent data, however, strongly suggest that a stimulation of microglia function, rather than inhibiting their function, might be useful in AD treatment.

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Figure 1. Release of GM-CSF by young microglia restores the A β uptake capacity of old microglia.

It is due to the high A β uptake capacity of neonatal microglia that in slices cultured from neonatal mice no A β plaques are formed even when A β is exogenously added. In cultured slices from 10- to 20-month-old APPPS1 animals, A β plaques are found and these slices contain microglia with impaired A β uptake capacity. In co-cultures of old APPPS1 slices together with slices from neonate wild-type animals, a significant removal of A β plaque is observable. The presence of neonate microglia restores the A β uptake capacity of old microglia in APPPS1 slices. Since supernatants from microglia-containing neonatal wild-type slices are sufficiently enhancing the A β uptake capacity tool, it can be concluded that this effect is due to a released microglia-derived factor. This factor was identified as GM-CSF, as the treatment of old APPPS1 slices with GM-CSF leads to the proliferation of old microglia, enhancement of their A β uptake capacity and reduction in A β plaque load.

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