

Bone-derived microglia clear amyloid plaques

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Alzheimer's disease (AD) is an incurable neurodegenerative disease and is the most common cause of dementia that affects elderly people (Izenberg, 2000). Today as citizens are living longer, AD is reaching epidemic proportions with no cure available (Tanzi and Bertram, 2005). In America, 4 million people are affected by this disease and it is estimated that the epidemic will jump 44 percent by the year of 2025 (Medline Plus, 2006). AD patients live debilitating lives of faulty memory, judgment, and reasoning (Tanzi and Bertram, 2005). However, a promising study published in *Neuron* by Simard et al. (2006) suggests a future therapeutic strategy. They employ stem cells that specifically target the amyloid deposits, the toxic culprit in this disease pathology.

When Alzheimer's disease strikes the brain, it makes three main aberrant structural changes. One change is the extensive loss of neurons in the hippocampus and neocortex. The second change is the accumulation of intracellular protein deposits called neurofibrillary tangles. The third change is the accumulation of extracellular protein deposits termed amyloid (A β , also called senile plaques, surrounded by damaged neurites (George-Hyslop and Westaway, 1999).

The build up of A β in the brain is considered to be a major cause toward AD pathogenesis. A β is naturally produced by the breakdown of a bigger protein called β -amyloid precursor protein (APP). However, in AD patients, the problem occurs when the APP is mutant. The mutation progresses the production of too much A β (Hardy and Selkoe, 2002).

Thus far, the research on amyloid plaques has shown that they influence significant immunological changes in their cellular environment. When A β deposits build up, they elicit an innate immune response on the central nervous system (CNS) (Monsonogo and Weiner, 2003). Specifically, they activate the microglia, which are the immune cells of brain. The inflammatory response triggers the microglia to surround the amyloid deposits. This behavior of microglia immune cells has been observed in the rodent transgenic model of AD (Malm et al., 2005).

Interestingly, the scientific community is in a debate over the role of microglia in Alzheimer's Disease. Since there is a large amount of microglia in the diseased brain, they must, undisputably, play an important pathological role. (Rogers et al., 2002). Studies show activated brain microglia to have the capacity to be either potentially neurotoxic or beneficial to the brain. In test tube studies, when cultured microglial cells encounter A β peptides they trigger an immune response and secrete high levels of proinflammatory cytokines. However, the secretion of cytokines in the brain would be fatal. (Rogers et al., 2002). On the other hand, test tube studies also show that the microglial cells play a positive role. They clear up cellular debris and certainly are capable of clearing A β deposits by phagocytosis (Wegiel et al., 2004).

Nevertheless, studying the role of microglia in AD animal model is more relevant than any study in the test tube. In AD mouse model, the outcome of clearing A β deposits by microglia has been questionable because A β deposits are abundant in the brain and form faster than they can be cleared by the microglia (Wegiel et al., 2004). Prior to the research done by Simard et al. (2006), the microglia have been shown to be inefficient at degrading A β deposits.

Now, in the study of AD using transgenic mice model, Simard et al. (2006) show that there are other efficient microglia of blood origin which specifically phagocytose amyloid plaques. Simard and colleagues demonstrate that the monocytes pass through the blood brain barrier of CNS and differentiate into microglia. These blood-derived microglia are shown to closely associate with A β deposits. In the AD affected region of the hippocampus, Simard et al. found bone marrow-derived microglia to colocalize with the β -amyloid 40/42.

Following the first evidence, Simard et al. (2006) test a very important question of whether blood-derived microglia are beneficial in slowing down the build up of amyloid plaques. They treat the undifferentiated blood derived cells with ganciclovir drug that impedes the cells differentiation into microglia. The scientists closely observe the changes in A β formation strictly when no blood-derived microglia are created. They discover that the size and the number of amyloid plaques increase with ganciclovir treatment.

In addition, they see a second type of non-blood derived (resident) microglia associate with A β deposits but unlike the blood microglia, they are not able to clear amyloid plaques. This observation seriously suggests that the blood-derived microglia are specific species of the brain immune cells better capable of removing the amyloid plaques and possibly further preventing the plaque formations.

Simard et al. (2006) observe that as A β deposits associate with bone marrow-derived microglia, an immune response is elicited. Astonishingly, this response happens to be concurrent with the decrease in the size and the number of amyloid plaques. As such, blood-derived microglia draws a beneficial mechanism. It is a converse of the response that resident microglia produce in which dangerous proinflammatory cytokines secrete.

Past in vivo experiments have shown that resident and blood-derived microglial cells are not distinguished in their function. Usually, these studies comment on the idea that microglia are incapable of phagocytosing amyloid plaques. However, Simard et al. (2006) make an attempt to clear up the confusion that exists in explaining the role of microglia. There are two types of microglia: resident microglia and blood-derived microglia. The latter perform a beneficial mechanism for the cell by carrying out phagocytosis and protecting the central nervous system from a neurodegenerative disease.

In the last decade, therapeutic methods of preventing and curing AD have failed. In the Simard et al. (2006) study, the bone marrow stem cells shine on a novel strategy of eliminating amyloid plaques to possibly treat AD patients (Figure 1). There is a strong belief now that the prospect of treating Alzheimer's Disease will come from learning more about how the immune response plays a role in the degenerative process (Monsonogo and Weiner, 2003).

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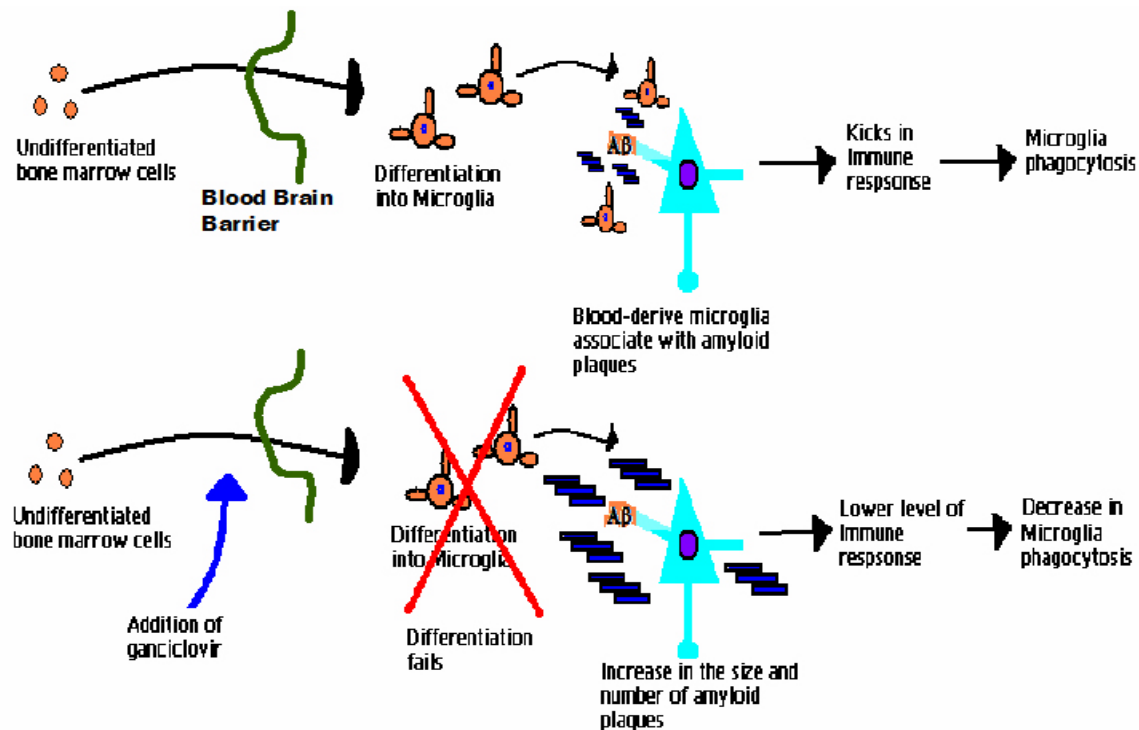


Figure 1: Blood-derived microglia specifically target amyloid plaques for elimination by phagocytosis.

Since the activation of blood-derived microglial cells create an immune response which reduces the size and the number of amyloid plaques, these microglial cells may be the key for AD therapy.

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