PERSPECTIVE

The therapeutic potential of mesenchymal stem cells in Alzheimer's disease: converging mechanisms

Mesenchymal stem cells (MSCs) are pluripotent stem cells isolated from various tissues, but mostly from bone marrow, adipose tissue, and umbilical cord blood. Well known for their mesenchymal lineages differentiation (*e.g.*, bone, cartilage and fat tissues), it was suggested that MSCs possess plasticity properties enabling them to differentiate into non-mesenchymal lineages. Indeed, several protocols claimed for differentiating MSCs to neurons *in vitro*, but concern was raised for the effectiveness and *in vivo* relevance of such differentiation. Thus, though their neurogenic differentiation properties are still in debate, they were nevertheless, suggested as candidates for treating neurodegenerative disorders such as Parkinson's diseases, multiple sclerosis and Alzheimer's disease (AD).

AD is a neurodegenerative disease resulting in cholinergic neuronal loss in general together with site specific lesions and pathologies such as impaired neurogenesis in the hippocampus. AD is characterized by two major pathological findings: the accumulation of extracellular plaques composed of mainly amyloid-β peptide (Aβ) and intracellular neurofibrillary tangles (NFT) composed of phosphorylated tau protein. Aβ is a product of an enzymatic cleavage of the APP transmembranal protein, present in neuron. Both its monomeric form and oligomeric aggregates exhibit neurotoxic properties, hence the degeneration of neurons in the disease. In addition to that, neuroinflammation is also involved in AD pathogenesis, where pro-inflammatory cytokines and cells reduce survival of neurons and promote neurodegeneration.

Originally, the potential ability of MSCs to differentiate to neural cells was the main drive to suggest them as a therapeutic approach for neurodegenerative diseases in general and AD in particular. As such, MSCs seemed relevant to the regeneration and replacement of lost neural cells. However, it has long been since recognized, that MSCs possess other properties potentially beneficial in prevailing the pathological mechanisms of AD. Thus, MSCs based therapy can not only regenerate damaged neuronal tissue but also prevent or stop the progression of the disease. Indeed, most of the *in vivo* studies conducted with MSCs have taken the later approach.

MSCs have remarkable ability to induce the rapid clearance of Aβ aggregates both *in vitro* and *in vivo*. Mechanistically, the clearance of Aβ deposits was attributed mainly to microglial cell activation, resulting from their interaction with MSCs (Lee et al., 2009). Furthermore, MSCs are able to recruit additional microglial cells from the bone marrow by the expression of CCL5 (Lee et al., 2012b). In this way, MSCs can prevent accumulation of Aβ plaques and potentially prevent the deterioration of the disease. Interestingly, a reduction in intracellular neurofibrillary tangles was also observed in these studies.

In a wide perspective, the activation of microglial cells, should be seen as a part of a broader effect of engrafted MSCs on the local immune environment. Microglial activation was accompanied by anti-inflammatory cytokine expression and reduced inflammatory response (Lee et al., 2012a). This should not be surprising since MSCs are well known for their immune-modulatory properties.

Hippocampal neurogenesis is badly affected in AD as the disease progresses, leading to impaired cognitive functions. Moreover, decrease of neurogenesis by direct Aβ injection was previously demonstrated. Adult neurogenesis is an important mechanism enabling neuroplasticity in the AD inflicted brain, necessary for preserving cognitive functions (Jellinger and Attems, 2013). It was previously postulated that adult hippocampal neurogenesis can compensate for the neuronal loss caused by AD pathology. Active neurogenesis can promote and account for neuroplasticity and neural circuitry rearrangement. In agreement with this argument, several studies indicated an increase in hippocampal neurogenesis in the early stages of the disease, as a compensating mechanism, whereas in later stages, neurogenesis is impaired (Mu and Gage, 2011). Indeed, in a recently published paper we were able to demonstrate a correlation between Aβ aggregates accumulation, following $A\beta_{25-35}$ oligomers injection to the lateral ventricle of mice, and compensating hippocampal neurogenesis (Hamisha et al., 2014). In our study, we observed an increase in newly formed neurons (expressing doublecortin) in the granular cell layer that was positively correlated with the number of Aβ aggregates seen in the same hippocampi in Aβ injected mice. Moreover, we showed that the increased neurogenesis eventually leads to normalized scores in the Morris water maze spatial learning paradigm.

An important property of MSCs, in this regard, is their ability to induce endogenous neurogenesis. Secretion of various neurotrophic factors by MSCs can result on one hand in neuroprotection and on the other hand in induction of neurogenesis by local neural stem cells and progenitors. As previously reported by our group and many others, MSCs engrafted into central nervous system (CNS) can enhance endogenous neurogenesis in the hippocampus in health and disease leading to improved behaviour (Tfilin et al., 2010). Since as mentioned above, impaired neurogenesis is evident in AD, increasing it may restore and preserve cognitive functions. Thus, targeting hippocampal neurogenesis as a potential therapeutic approach for AD was suggested and well demonstrated in several animal studies (Shruster and Offen, 2014). Furthermore, adipose tissue-derived MSCs were indeed shown to increase hippocampal neurogenesis following intracerebral injection to the hippocampi of the APP/PS1 transgenic mouse model of AD (Yan et al., 2014).

It is noteworthy that microglial cell activation may in turn regulate neurogenesis *via* secretion of growth factors and cytokines, depending on the type of activation/neuroinflammation they are exposed to (Butovsky et al., 2006). One can thus see how the various properties of MSCs, *i.e.*, modulation of neuroinflammation, activation of microglia and induction of neurogenesis, interact together, cross-influence each other and converge to yield a powerful effect to counter AD pathology.

In this context, taking into account the converging effect of MSCs, a recently published observation from our study deserves a special attention and interpretation. We have found that MSCs injected into the lateral ventricle with $A\beta_{25-35}$ oligomers have induced Aβ clearance and engrafted, among other sites, to the choroid plexus (Hamisha et al., 2014). In this observation, never reported previously, fluorescently labelled (DiI) MSCs were found to engraft in the choroid plexus with some cells even displaying the morphology of ependymal cells (**Figure 1**). This unique pattern of engraftment may suggest an additional property of MSCs with regard to AD pathology. Is there a possible link between this engraftment pattern of MSC and the observed clearance of Aβ? The choroid plexus has been suggested to play

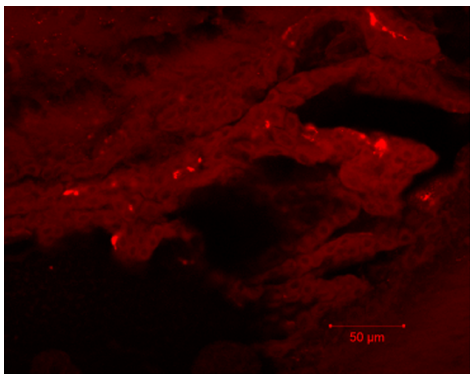

Figure 1 Mesenchymal stem cells (MSCs) engraft to the choroid plexus in amyloid-β peptide injected mice.
DiI (1,1′-dioctadecyl-3,3,3′3′-tetramethylindocarbocyanine perchlorate) labelled MSCs (red fluorscence) engrafted to the choroid plexus of $A\beta_{25–35}$ oligomers 8 days following injection into the lateral ventricle.

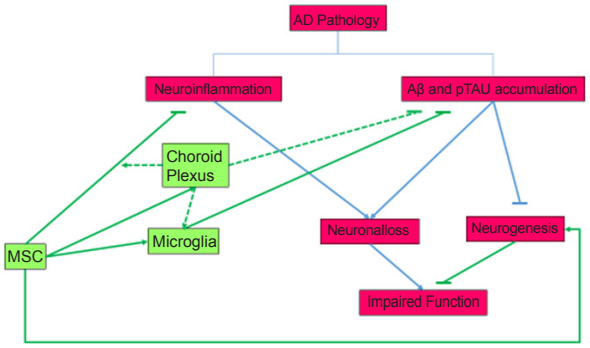

Figure 2 The converging mechanisms of mesenchymal stem cells (MSCs) in Alzheimer's disease (AD).
A schematic diagram outlining the relations between AD pathologies (in red boxes and blue lines) and the therapeutic properties of MSCs (green boxes and lines). Dashed lines represent hypothetical interaction.

a key role in mediating clearance of Aβ monomers from the CNS to the cerebrospinal fluid and maintaining low levels of Aβ in the CNS. Thus, it was also suggested that the choroid plexus may play a role in AD pathology and possibly also in treatment (Serot et al., 2012). While a further study should engage the role and function of engrafted MSCs in the choroid plexus. It is possible that MSCs can influence the clearance properties of the choroid plexus, therefore, providing an additional mechanism for clearing Aβ other than microglial activation.

Furthermore, in a different aspect, the choroid plexus has been also suggested as a surveillance niche for the immune system in the CNS, regulating immune cell activation and neuroinflammation (Schwartz and Shechter, 2010). In this respect, the engraftment of MSCs to the choroid plexus may potentiate their modulatory effect on neuroinflammation and microglia activation. It is also conceivable that such modulation occurring in the choroid plexus may in turn also influence hippocampal neurogenesis, though direct engraftment of MSCs to the hippocampus was also observed. One can further postulate that the choroid plexus may provide the anatomical, cellular and biochemical niche for MSC's converging mechanism (**Figure 2**).

In conclusion, studies in recent years have found that MSC's therapeutic role in neurodegenerative diseases is much more complex than originally thought. While MSCs were perceived for years as eligible only for cell replacement purposes, the role of their interaction with the immune system and host tissue progenitors was eventually recognized as having greater significance in mediating their therapeutic effect (Tfilin et al., 2010; Lee et al., 2012a). Indeed, we still far from fully understand MSC's biology and cellular interactions. Better understanding will enable us to better comprehend the therapeutic potential of MSC and allow us to design new therapeutic strategies. Moreover, better understanding of MSC's biology may eventually shed a new light on the role and functions of stem cells in general, allowing a new paradigm for studying the role of adult stem cells in physiology and therapy.

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