Phagocytosis and Presentation of Amyloid β-Associated Antigens by Monocyte-Derived Macrophages in AD Pathology

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Background: Hydrophobic Aβ peptides require a carrier for transport through the interstitial fluid, CSF, lymphatic fluid and blood. Biomacromolecules, such as LRP1, RAGE and some of plasma proteins are considered as Aβ carriers and participate in different transport stages. However, the possibility of peripheral immune cells as carriers was simply ignored because they are too large to cross the blood-brain barrier. The current study revisits the puzzle of whether human monocyte-derived macrophages can remove Aβ from the brain and come to the periphery for antigen presentation.

Methods:
1) Of the leukocytes tested, monocytes, especially CD14+CD16+ monocytes, were identified by flow cytometry in vitro. Aβ-carrying monocyte-derived macrophages (MDM) in human blood circulation and cerebrospinal fluid (CSF) were identified and characterized.
2) The levels of leukocytes carried by MDM were compared between AD patients and cognitively normal (CN) controls.
3) Intracerebroventricular injection of CFSE-labeled PBMC into AD mice was used to track whether there is an egress for CSF MDM to return to the peripheral blood.

Results:
1) Of the leukocytes tested, monocytes, especially CD14+CD16+ monocytes, were found to be the predominant cell type that phagocytizes Aβ peptides (Fig. 1a-b). Likewise, CD14+CD16+ monocytes were found to carry Aβ in human blood circulation (Fig. 1c-d) and CSF (Fig. 1e), and further immunophenotypes indicated that these cells were a type of MDM (Fig. 1f).

Figure 1. Identification of Aβ-carrying MDM in blood and CSF.

2) In 154 individuals (Table 1), the levels of Aβ carried by blood monocytes were reduced by 26% in AD compared with control (Fig. 2a), and this change was correlated with the subject’s brain PET Aβ score (Centiloid), episodic memory and PACC score. The percentage of W0-2+ monocytes in total monocytes also decreased in MCI and AD-dementia compared with CN and correlated with Centiloid, EM and PACC score (Fig. 2b).

Table 1. Demographics of the study cohort.

<table>
<thead>
<tr>
<th>Composite PACC score (mean (SD))</th>
<th>MMSE (mean (SD))</th>
<th>ApoE genotype (% E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, E4/E4)</th>
<th>Number of Participants (n)</th>
<th>Sex (% M, F)</th>
<th>Clinical Classification (% MCI, CN, AD)</th>
<th>Age (mean (SD))</th>
<th>Sex (% M, F)</th>
<th>Clinical Classification (% MCI, CN, AD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.16 (0.54)</td>
<td>28.05 (2.38)</td>
<td>0.64 (0.62)</td>
<td>12.89 (3.08)</td>
<td>73.05 (6.93)</td>
<td>0.05 (1.10)</td>
<td>10.83 (2.17)</td>
<td>72.43 (7.26)</td>
<td>0.01 (0.96)</td>
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<tr>
<td>0.01 (0.96)</td>
<td>24.56 (5.24)</td>
<td>0.18 (0.29)</td>
<td>10.83 (2.17)</td>
<td>72.43 (7.26)</td>
<td>0.05 (1.10)</td>
<td>10.83 (2.17)</td>
<td>72.43 (7.26)</td>
<td>0.01 (0.96)</td>
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<tr>
<td>0.35 (0.25)</td>
<td>15.33 (3.54)</td>
<td>0.05 (1.10)</td>
<td>10.83 (2.17)</td>
<td>72.43 (7.26)</td>
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3) The adoptive CFSE+ PBMC were found in the peripheral blood and deep cervical lymph nodes (dcLN) of 85% AD mice two days after injection.

Figure 2. Blood monocyte-carried Aβ decreased in AD.

Figure 3: Detection of adoptive CFSE+ PBMC in blood and dcLN.

Conclusions: Our study investigated the potential mechanism of MDM-based Aβ transport between CNS and periphery. The findings from our study shed light on how peripheral monocytes and phagocytosis contributes to AD pathology. Moreover, it may have important implications for understanding Aβ-associated antigen presentation and T- and B-cell activation in dcLN.

Figure 4: Phagocytosis and presentation of Aβ in MDM.