Profiling of specific gene expression pathways in peripheral cells from Alzheimer's disease patients


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BACKGROUND

-Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by progressive loss of memory and decline of cognitive functions. Worldwide research has led to a growing knowledge of the genetics and molecular pathogenesis of AD, indicating that pathophysiological brain alterations occur decades before clinical signs and symptoms of cognitive decline appear.

-Currently, AD diagnosis is correctly performed by use of several biomarkers, such as structural and/or functional imaging (MRI, PET), cerebrospinal fluid (CSF) protein detection (β-amyloid, tau and p-tau) in accordance with Dubois criteria [1]. However, these biomarkers are invasive and expensive and in this framework, the identification of new peripheral biomarkers would be of critical importance in order to improve AD diagnosis.

-To date, there is increasing evidence supporting a link between AD and insulin dysfunction [2,3].

To perform a whole gene expression profiling in peripheral cells from patients with MCI, Prodromal AD (MCI with AD CSF profile) and AD compared with controls

MATERIALS & METHODS

-Wide analysis with Sabioscience arrays in:
  - 10 MCI (of which 5 prodromal AD)
  - 7 AD patients (3 PSEN1 Met146Leu mutation carriers)
  - 4 healthy controls

CONCLUSIONS

-This is the first attempt to test gene expression profile in a cohort of very mild AD (MCI with AD CSF signature)
-We observed a generalized up-regulation in patients compared with controls and this data seem to be much evident in prodromal AD patients.
-Particularly, we observed a dysregulation of Insulin and Insulin receptor gene expression also in the validation cohort.
-Recently, an active role of insulin signal pathway was shown in AD pathogenesis
-In this context, our results suggest a possible future use of these molecules as peripheral biomarkers for early diagnosis

FUTURE PLAN

-To enlarge validation cohort (MCI and Prodromal AD)
-To replicate validation analysis for INS and INSR gene expression with RNA extracted from CSF cells
-To investigate a possible brain insulin resistance in AD patients by testing the role of insulin signaling (i.e. to evaluate CSF soluble phosphorylated IRS1 levels)

RESULTS

Screening:

- Normal CSF biomarkers
  - High Abeta
  - Low tau
- AD-like CSF biomarkers
  - Low Abeta
  - High tau

- Generalized up-regulation in patients compared with controls.

<table>
<thead>
<tr>
<th>Gene</th>
<th>MCI</th>
<th>AD prodromal</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACHE</td>
<td>5.57</td>
<td>12.09</td>
<td>18.27</td>
</tr>
<tr>
<td>APLP1</td>
<td>4.29</td>
<td>6.60</td>
<td>13.26</td>
</tr>
<tr>
<td>IL1A</td>
<td>1.78</td>
<td>3.68</td>
<td>8.99</td>
</tr>
<tr>
<td>INS</td>
<td>5.38</td>
<td>P&lt;0.05</td>
<td>39.20</td>
</tr>
<tr>
<td>INSR</td>
<td>-1.68</td>
<td>1.49</td>
<td>3.47</td>
</tr>
</tbody>
</table>

INS: encodes for insulin and it is located on chromosome 11p15.5

INSR: encodes for insulin receptor (chromosome 19p13.3). After removal of the precursor signal peptide, the insulin receptor precursor is post-translationally cleaved into two chains (alpha and beta) that are covalently linked.

Validation:

- Up-regulation was confirmed for both genes in the validation population (data represented as mean ± SEM)

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<th>AD</th>
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</thead>
<tbody>
<tr>
<td>INS</td>
<td>1.556 ± 0.26 versus ctrls 0.4256 ± 0.12 P=0.0009</td>
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<tr>
<td>INSR</td>
<td>3.545 ± 0.5 versus ctrls 2.089 ± 0.35 P=0.0372</td>
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References