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Short Communication

sTREM2 and GFAP Mediated the Association of IGF-1 Signaling Biomarkers with Alzheimer's Disease Pathology

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Abstract. Defects in insulin-like growth factor 1 (IGF-1) signaling is a key contributor to Alzheimer's disease (AD). However, the mechanism of how IGF-1 signaling relates to AD remained unclear. Here, we investigated the association of IGF-1 signaling associated biomarkers with AD pathology, sTREM2, and GFAP. Finally, insulin-like growth factor binding protein 2 (IGFBP-2) was associated with AD pathology, and the association was partly medicated by sTREM2 ($A\beta_{42}$, $\beta = 0.794$, $p = 0.016$; T-tau, $\beta = 0.291$, $p < 0.001$; P-tau_{181}, $\beta = 0.031$, $p < 0.001$) and GFAP (T-tau, $\beta = 0.427$, $p < 0.001$; P-tau_{181}, $\beta = 0.044$, $p < 0.001$). It suggested that sTREM2 and GFAP mediated the relationship between IGF-1 signaling and AD pathology.

Keywords: AD pathology, Alzheimer's disease, GFAP, IGF-1 signaling, IGFBP-2, sTREM2

INTRODUCTION

Alzheimer's disease (AD) is characterized pathologically by aberrant senile plaques (amyloid deposition) and neurofibrillary tangles (tau phosphorylation), and clinically by cognitive decline and behavioral disorders [1]. AD is the common comorbidity of type 2 diabetes mellitus (T2DM) and T2DM is the crucial risk factor for dementia and AD [2, 3]. To date, emerging evidence identified that insulin resistance, the core mechanism underlying T2DM, also contributes to the onset of AD [4, 5]. However, the mechanism underlying the contribution of insulin resistance to AD pathogenesis was still unclear. Recently, it was observed that insulin resistance activated microglia and astrocytes to be involved in the biological process of AD pathology [amyloid-β (Aβ) and tau] in animal models [2]. Thus, it was possible that insulin resistance signaling, such as impairments in insulin signaling or insulin-like growth factor 1 (IGF-1) signaling, correlates with the activity of microglia and astrocytes and mediates the development of AD pathology in human brain.

Impaired IGF-1 signaling was the core feature of insulin resistance and was reported to be related to amyloid plaque, tau phosphorylation, and higher incidence of AD in previous studies [6, 7]. Insulin like growth factor binding proteins (IGFBPs) limit IGF-1 actions by altering the affinity of IGF-1 to their

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receptors. It was also observed that IGFBPs were correlated with the levels of Aβ and tau pathology previously [8, 9]. In addition, soluble triggering receptor expressed on myeloid cells 2 (sTREM2) is a soluble form of TREM2 and plays roles in modulating immune responses and activating microglia during the phagocytosis of Aβ pathology [10–12]. Glial fibrillary acidic protein (GFAP) is an intermediate filament mainly expressed in astrocytes. GFAP is overexpressed in reactive astrocytes affecting neuroinflammatory and is associated with Aβ and tau pathology in AD brain [13, 14]. Based on the above findings, we proposed that IGF-1 signaling associated markers are related to AD pathology, and the associations may be mediated by microglia and astrocyte markers. Here, we aimed to extract the results of IGF-1 and IGFBPs from CSF proteomics data in the Alzheimer's Disease Neuroimaging Initiative (ADNI) database to investigate the associations of IGF-1 signaling associated markers (IGF-1 and IGFBPs) with AD pathology, sTREM2 and GFAP, and to identify whether sTREM2 and GFAP mediated the associations of IGF-1 signaling with AD pathology in brain.

MATERIALS AND METHODS

Participants

All participants were from the ADNI database (https://adni.loni.usc.edu). The detailed full inclusion/exclusion criteria can be obtained on their website. Participants underwent systematic neuropsychological evaluations and were offered biological samples such as blood and cerebrospinal fluid (CSF) samples. The ADNI project was conducted in link with the Declaration of Helsinki. The study was approved by the Institutional Review Board of Qingdao Municipal Hospital.

CSF IGF-1 signaling associated markers

The results of IGF-1 and IGFBPs were from "Biomarkers Consortium ADNI CSF QC Multiplex data.csv" online (https://loni.usc.edu/). Given that the results of IGF-1 did not pass the quality control of data, only the results of IGFBP-2 were extracted to perform the next analysis. The measurements of CSF proteomics were based on Luminex immunoassay platform and improved by Rules Based Medicine to test inflammatory, lipid, and other molecules. Detailed information on CSF proteomics and quality control can be found in the content of "Biomarkers Consortium Data Primer" online.

AD core biomarkers

In this study, $A\beta_{42}$, T-tau, and P-tau_{181} were obtained from the ADNI dataset "Upen_Biomk9.csv" online. The AD core biomarkers were analyzed by the electrochemiluminescence immunoassays (ECLIA) Elecsys total-tau CSF, the Elecsys phospho-tau(181P) CSF, and the Elecsys β-amyloid (1–42) CSF on an automatic Elecsys instrument. CSF sample collection, processing, and quality control of $A\beta_{42}$, T-tau, and P-tau_{181} were described elsewhere [15]. Based on the previous study, we used CSF $A\beta_{42} \leq 976.6$ pg/mL, P-$tau_{181} \geq 21.8$ pg/ml, and T-tau ≥ 245 g/ml as thresholds to identify abnormal levels [16].

CSF sTREM2 and GFAP

The measurement of CSF sTREM2 was performed with the MSD platform-based assay, which was previously reported and validated [17]. The sTREM2 data were from the file "CSF soluble triggering receptor expressed on myeloid cells 2 (sTREM2) and progranulin (PGRN)" online. The GFAP data were from the ADNI dataset "Biomarkers Consortium CSF Proteomics MRM Date" online. The methods of measurement were CSF MRM multiple panel tests developed by Caprion Proteomics in collaboration with the Biomarker Consortium Project Team. The information can be found on the website of ADNI.

Statistical analyses

Based on the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria [18], the participants with normal $A\beta_{42}$ (A), P-tau_{181} (T), and T-tau (N) levels are classified as the stage 0; the participants with abnormal $A\beta_{42}$ (A), normal P-tau_{181} (T) and normal T-tau (N) were classified as the stage 1; the participants with abnormal $A\beta_{42}$ (A), and abnormal P-tau_{181} (T) or abnormal T-tau (N) levels as the stage 2; and participants with normal $A\beta_{42}$, but abnormal P-tau_{181} or abnormal T-tau levels are classified as suspected non-Alzheimer's pathophysiology (SNAP) group.

The differences among the four groups were computed using the one-way analysis of variance (ANOVA) for continuous variables and chi-square analysis for categorical variables. We assessed the

association of IGFBP-2 (independent variable) with AD core biomarkers, sTREM2 and GFAP using a multiple linear regression model with age, sex, years of education, and APOE ε4 carrier status as covariates. Mediation analyses were fitted to investigate whether the association between IGFBP-2 and AD pathology was mediated by sTREM2 and GFAP, and the indirect effect was computed with 10,000 bootstrapped iterations. p value < 0.05 was considered significant.

RESULTS

Characteristics of participants

In the 233 participants who underwent the measurement of CSF IGFBP-2, AD core biomarkers ($A\beta_{42}$, T-tau, and P-tau181), sTREM2 and GFAP, 43 participants were in the stage 0, 33 participants were in the stage 1, 122 participants were in the stage 2, and 35 participants were in the SNAP group. The demographical and clinical characteristics are described in Table 1. There were no differences in terms of age, gender, and educational years between the four groups. As expected, the levels of AD core biomarkers ($p < 0.01$) showed significant differences between the four groups, and the proportion of APOE ε4 carriers ($p < 0.01$) was different among the four groups. In addition, the levels of sTREM2 ($p < 0.01$) and GFAP ($p < 0.01$) in CSF showed remarkable differences across the four groups. Finally, there is a significant difference on the level of IGFBP-2 in CSF between the four groups.

IGFBP-2 is associated with AD core biomarkers, sTREM2, and GFAP

The correlations between CSF IGFBP-2, AD core biomarkers, sTREM2, and GFAP were tested in 233 participants (Fig. 1A). We found that the elevated IGFBP-2 level was associated with the higher levels of GFAP ($\beta = 0.005$, 95% CI: 0.001–4.732, $p < 0.001$) (Fig. 1B) and sTREM2 ($\beta = 24.408$, 95% CI: 4.659–5.239, $p < 0.001$) (Fig. 1C). Increased IGFBP-2 level was remarkably correlated with higher levels of P-tau_{181} ($\beta = 0.122$, 95% CI: 0.027–4.529, $p < 0.001$) (Fig. 1D) and T-tau ($\beta = 1.186$, 95% CI: 0.236–5.028, $p < 0.001$) (Fig. 1E). Further, these associations between these biomarkers still existed in sensitivity analyses with various covariates regressed out and in the mild cognitive impairment (MCI) group (Supplementary Table 1), which verified the robustness of our results. In addition, sTREM2 and GFAP were also markedly related to the levels of AD core biomarkers (Fig. 1A).

sTREM2 and GFAP mediate the effects of IGFBP-2 on AD pathology

We investigated whether the connections between IGFBP-2 and AD core biomarkers were mediated by sTREM2 or GFAP. The association between IGFBP-2 and $A\beta_{42}$ was partly mediated by sTREM2 ($\beta = 0.794$, 95% CI: 0.124 – 1.610, $p = 0.016$), but was not mediated by GFAP ($\beta = 0.072$, $p = 0.815$) (Fig. 2A). The connection between IGFBP-2 and T-tau was partly mediated by sTREM2 ($\beta = 0.291$, 95% CI: 0.122 – 0.500, $p < 0.001$) and GFAP ($\beta = 0.427$, 95% CI: 0.222 – 0.680, $p < 0.001$) (Fig. 2B). Likewise, the relationship between IGFBP-2 and P-tau_{181} is partially mediated by sTREM2 ($\beta = 0.031$, 95% CI: 0.011 – 0.060, $p < 0.001$) and GFAP ($\beta = 0.044$, 95% CI: 0.022 – 0.070, $p < 0.001$) (Fig. 2C).

DISCUSSION

Our study showed that IGFBP-2 was significantly correlated with AD core biomarkers, sTREM2 and GFAP. Besides, sTREM2 was significantly associated with the levels of $A\beta_{42}$, T-tau, and P-tau_{181}, and GFAP was markedly related to the levels of T-tau and P-tau_{181}. Next, we found that sTREM2 mediated the effects of IGFBP-2 on Aβ pathology (Aβ in CSF) and tau pathology (P-tau_{181} and T-tau in CSF), and GFAP partially mediated the effect of IGFBP-2 on tau pathology (P-tau_{181} and T-tau in CSF). These findings suggested that IGFBP-2 may correlate with the AD pathology as it is associated with the levels of sTREM2 and GFAP in CSF.

It has been documented that insulin resistance is the risk factor for incidence of AD [4, 5]. Deficits in IGF-1 signaling were the critical cause of insulin resistance [6, 19], and IGFBP-2 was involved in the IGF-1 signaling pathway by binding IGF-1 with high affinity. To date, epidemiological studies identified that both IGF-1 and IGFBP-2 were significantly associated with an increased risk of AD in Framingham prospective cohort [7, 20], and IGF-1 signaling associated molecules co-occurred with amyloid plaques in the hippocampus and cerebellar cortex in postmortem studies [5]. In addition, IGF-1 signaling was reported to regulate the change of AD pathology through altering the action of microglia and astrocytes in animal models [2]. Here, our study found

Table 1
The demographic and clinical characteristics of participants

	Stage 0	Stage 1	Stage 2	SNAP	*p*
Number of individuals	43	33	122	35	
Age (y), mean (sd)	75.3 (5.35)	75.3 (5.52)	74.6 (7.27)	77.0 (7.00)	0.312
Female, n (%)	15 (34.9%)	9 (27.3%)	56 (45.9%)	13 (37.1%)	0.205
Education (y), mean (sd)	15.6 (2.97)	15.5 (3.80)	15.7 (3.02)	15.9 (2.88)	0.957
APOE ε4 carriers, n (%)	4 (9)	15 (46)	89 (73)	6 (17)	<0.001
$A\beta_{42}$ (pg/ml), mean (sd)	1445 (256)	642 (194)	606 (168)	1695 (613)	<0.001
T-tau (pg/ml), mean (sd)	192 (31.4)	177 (34.4)	368 (107)	332 (106)	<0.001
P-tau_{181} (pg/ml), mean (sd)	16.9 (2.82)	16.2 (3.61)	37.4 (12.5)	30.6 (12.1)	<0.001
GFAP (pg/ml), mean (sd)	11.0 (0.37)	10.9 (0.56)	11.2 (0.54)	11.3 (0.46)	0.001
sTREM2 (pg/ml), mean (sd)	4,451 (2130)	3,074 (1292)	4,729 (2592)	5,658 (2016)	<0.001
IGFBP-2 (ng/ml), mean (sd)	102 (18.7)	95.8 (15.9)	109 (38.8)	118 (32.4)	0.027

Stage 0, normal $A\beta_{42}$ with normal P-tau_{181} and T-tau level; Stage 1, abnormal $A\beta_{42}$ with normal P-tau_{181} and normal T-tau level; Stage 2, abnormal $A\beta_{42}$ with abnormal P-tau_{181} or abnormal T-tau level; SNAP, abnormal P-tau_{181} or abnormal T-tau but with normal $A\beta_{42}$; sd, standard deviation; $A\beta_{42}$, amyloid-β_{1-42}; T-tau, total-tau; P-tau_{181}, phosphorylated-tau; sTREM2, soluble TREM2; GFAP, glial fibrillary acidic protein; IGFBP-2, insulin-like Growth Factor-Binding Protein 2; SNAP, suspected non-Alzheimer's pathophysiology.

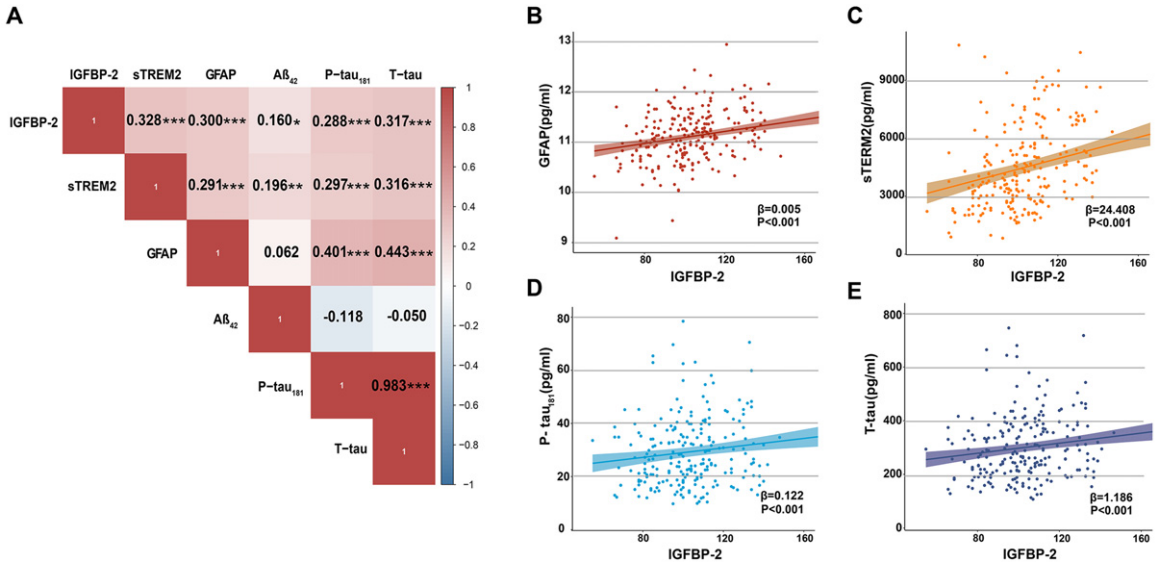

Fig. 1. Associations of IGFBP-2 with AD core biomarkers, sTREM2 and GFAP. A) The partial correlation between IGFBP-2 and AD core biomarkers, sTREM2 and GFAP with age, sex, years of education, and *APOE* ε4 status as control variables. B) IGFBP-2 was associated with the level of sTREM2 in a multiple regression model ($\beta = 0.005$, $p < 0.001$). C) IGFBP-2 was associated with the level of GFAP in a multiple regression model ($\beta = 24.408$, $p < 0.001$). D) IGFBP-2 was associated with T-tau in a multiple regression model ($\beta = 0.122$, $p < 0.001$). E) IGFBP-2 was associated with P-tau_{181} in a multiple regression model ($\beta = 0.186$, $p < 0.001$). The multiple linear regression model was adjusted for age, sex, years of education, and *APOE* ε4 status. IGFBP-2, Insulin like growth factor binding protein 2; $A\beta_{42}$, amyloid-β_{1-42}; P-tau_{181}, phosphorylated tau protein; T-tau, total tau protein; sTREM2, soluble triggering receptor expressed on myeloid cells 2; GFAP, glial fibrillary acidic protein. *<0.05, **<0.01, ***<0.001.

that IGF-1 signaling associated biomarker (IGFBP-2) was related to AD pathology, and the relationship was mediated by sTREM2 and GFAP. These findings provided new evidence for the mechanisms of how IGF-1 signaling was related to the change of AD pathology.

The study was designed to test the association between IGF-1 signaling, AD pathology, and sTREM2 and GFAP. At first, we intended to extract the results of IGF-1 and IGFBPs from the CSF proteomics data to detect their associations with AD core biomarkers, whereas the results of IGF-1 failed to pass the quality control of proteomics data, and only IGFBP-2 was used in our study. Age, sex, and other factors were considered as covariates in our analyses due to their effects on IGFBP-2 and other markers. Moreover, it was possible that the level of IGFBP-2 was affected by special diseases (e.g., diabetes and

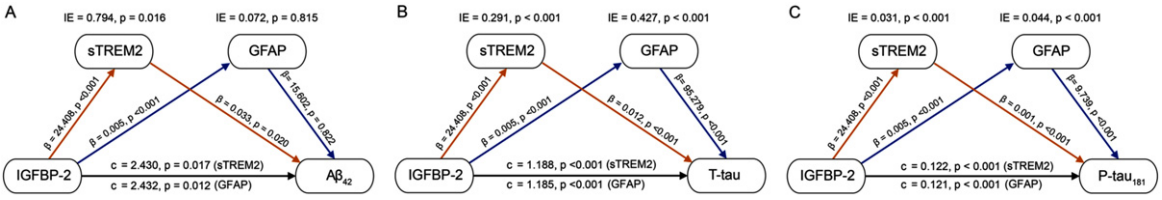

Fig. 2. Mediation effects of sTREM2 and GFAP on the link between IGFBP-2 and AD pathology. A) Mediation effects of sTREM2 ($\beta = 0.794$, $p = 0.016$) and GFAP ($\beta = 0.072$, $p = 0.815$) on the association between IGFBP-2 and $A\beta_{42}$. B) Mediation effects of sTREM2 ($\beta = 0.291$, $p < 0.001$) and GFAP ($\beta = 0.427$, $p < 0.001$) on the association between IGFBP-2 and T-tau. C) Mediation effects of sTREM2 ($\beta = 0.031$, $p < 0.001$) and GFAP ($\beta = 0.044$, $p < 0.001$) on the association between IGFBP-2 and P-tau_{181}. The effect sizes and p values were calculated in the mediation analyses with 10,000 bootstrapped iterations, which showed that cerebrospinal fluid sTREM2 or GFAP partly mediated the association between IGFBP-2 and AD core biomarkers. IGFBP-2, Insulin like growth factor binding protein 2; $A\beta_{42}$, amyloid-β_{1-42}; T-tau, total tau protein; P-tau_{181}, phosphorylated tau protein; sTREM2, soluble triggering receptor expressed on myeloid cells 2; GFAP, glial fibrillary acidic protein; IE, indirect effect.

hypertension) and medication history. We analysed the associations between IGFBP-2 and these diseases to test this possibility. Finally, neither diabetes ($\beta = 0.990$, $p = 0.447$) nor hypertension ($\beta = 1.006$, $p = 0.172$) was associated with the level of IGFBP-2 after controlling for age and sex. Additionally, due to limited information on medication history in the ADNI database, we did not investigate the effects of medication history on the content changes of these CSF biomarkers.

sTREM2 is the proteolytic product from TREM2, a transmembrane receptor expressed by microglia, and the level of sTREM2 in CSF could reflect the activity of microglia in central nervous system (CNS). It has been established that sTREM2 could regulate the amyloid pathology and neurodegeneration in CNS [2, 21]. Moreover, GFAP is generated from astrocytes and the level of GFAP in CSF was in line with the activity of astrocytes in brain. Similarly, GFAP was identified to be involved in the AD pathology (amyloid and tau pathology) in CNS [22, 23]. Further, sTREM2 and GFAP were recently identified to be potential diagnostic biomarkers for AD owning to their strong association with AD pathology [22, 24, 25]. Our study showed that sTREM2 and GFAP mediated the association between IGFBP-2 and AD pathology, which supported the hypotheses that insulin resistance could regulate the activation of microglia and astrocyte to participate in the AD pathology.

In summary, this study found that CSF IGFBP-2 was related to AD pathology, and the relationship was partly mediated by sTREM2 and GFAP. These findings elucidate that IGF-1 signaling correlates with AD pathology for it is related to sTREM2 and GFAP in brain. However, this investigation only focused on IGFBP-2, and it was necessary to explore the mechanisms of how other markers in the IGF-1/insulin signaling pathway were related to AD pathology in future.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

The dataset supporting the conclusions of this article is available in the ADNI site, https://adni.loni.usc.edu/.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-220725.

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