

hsa_circ_LPAR1 and hsa_circ_AXL as the most promising circRNAs to be validated as biomarkers for Alzheimer's disease: an *in silico* study

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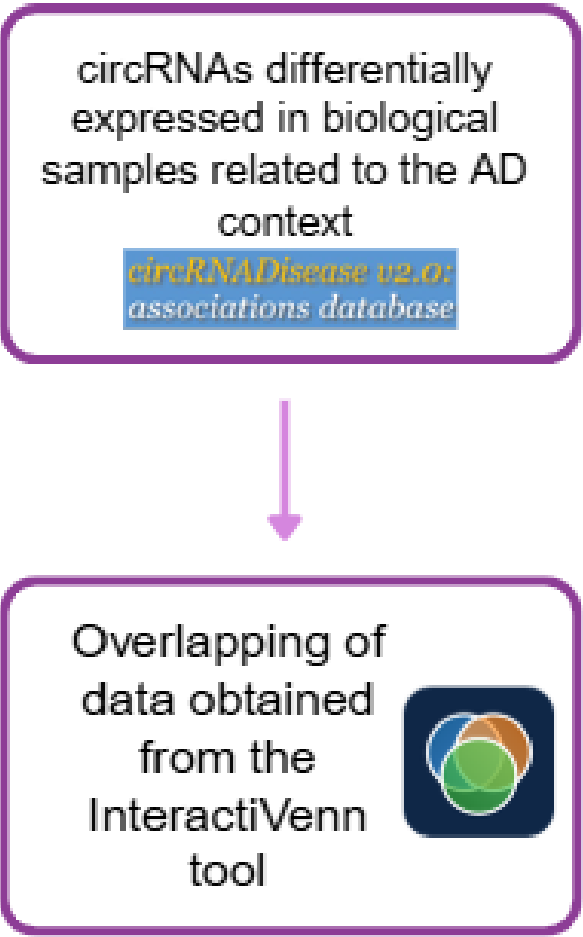
The present study aimed to identify the most promising circRNAs that could serve as biomarkers for clinical outcomes in AD using an *in silico* approach.

INTRODUCTION

- In Brazil, there has been an increase in mortality rates due to Alzheimer's disease (AD), which is characterized by the accumulation of insoluble β -amyloid and tau proteins in the brain, leading to progressive neurodegeneration and short-term memory deficit;
- This clinical sign and such proteins evaluation by imaging exams and in liquor compose AD diagnosis. Blood p-tau dosages can be an alternative to invasive and expensive diagnosis, nevertheless, its higher depuration difficult its detection;
- In this context, the clinical validity of the circulating biomarkers described so far for AD remains limited;
- Concurrently, circular RNAs (circRNAs), a class of long non-coding RNAs, are emerging as more stable biomarkers in various body fluids across numerous human pathologies. However, studies exploring the role of circRNAs in AD are still scarce.

METHODS

- Based on *in silico* strategies, the search for the circRNAs of interest was conducted in the experimentally validated database *circRNADisease* v2.0, using the "Search by Disease" field;
- All circRNAs found in this search were extracted without applying filters related to the type of method or biological sample, with data overlap performed using the *InteractiVenn* tool.



RESULTS AND CONCLUSIONS

- A total of 41 circRNAs were detected with significantly altered expression levels in cell lines and/or clinical samples (CL-CS) related to AD;
- Notably, a greater number of different studies identified 2 specific circRNAs (hsa_circ_LPAR1 and hsa_circ_AXL) upregulated in CL-CS samples. Remarkably, each previous study employed different nomenclatures for these circRNAs (hsa_circ_LPAR1 = hsa_circ_0003611; and hsa_circ_AXL = hsa_circ_0002945 = Circ_0002945);
- Considering that circRNAs can act as "sponges" for miRNAs, it was found that hsa_circ_LPAR1 has been reported as a sponge for hsa-miR-212-3p and hsa-miR-885-5p, while hsa_circ_AXL modulates hsa-miR-328, hsa-miR-1306-5 and hsa-miR-431-5p (**Table 1**)

Table 1. Main previous findings related to the two specific circRNAs most frequently reported in the literature as differentially expressed in the context of AD in humans.

circRNA nomenclature	Nomenclature by circID	Other synonyms	Host Gene	miRNA regulated by this circRNA	Method	Expressed in	Sample type details	Associated target	Association of circRNA	Biological function	Molecular mechanism	Description	PubMed ID
hsa_circ_LPAR1	hsa_circ_0003611	Not available	LPAR1	Not available	qPCR, Microarray	Uterus (cell)	Tissue	Not available	Not available	Not available	Not available	By RT-qPCR, circ-LPAR1, circ-AXL, and circ-GPR124 were increased, whereas circ-FoxO1, circ-HIF1A, circ-FoxO3, circ-FoxO4, and circ-FoxO6 were decreased in AD patients compared with controls subjects.	14911771
hsa_circ_AXL	hsa_circ_0002945	Not available	AXL	Not available	qPCR	Uterus (cell)	Tissue	Not available	Not available	Not available	Not available	Not available	14911771
hsa_circ_LPAR1	Not available	circ-LPAR1	LPAR1	hsa-miR-212-3p	qPCR	Uterus (cell)	Tissue, Cell lines (SK-N-SH, SK-N-SI)	14911771	14911771	Knockdown of circ-LPAR1 significantly reduced hsa-miR-212-3p-induced neuronal apoptosis, differentiation, and injury under Abeta25-35 stimulation.	circ-LPAR1 competitively bound to hsa-miR-212-3p to release its target (BACE1). Rescue experiments suggested that hsa-miR-212-3p induction increased circ-LPAR1 expression, affecting neuronal apoptosis and neuronal injury under Abeta25-35 stimulation.	Circ-LPAR1 promotes Abeta25-35-induced apoptosis, differentiation, and neuronal injury in SK-N-SH and SK-N-SI cells, and volatile stress in SK-N-SH cells. Circ-LPAR1 may serve as a potential therapeutic target for AD.	14911771
hsa_circ_AXL	Not available	circ-AXL	AXL	hsa-miR-328	qPCR	Uterus (cell)	Cell lines (SK-N-SH, SK-N-SI)	14911771	Not available	Circ-AXL overexpression increased neuronal cell apoptosis, differentiation, and injury under Abeta25-35 stimulation. Circ-AXL negatively regulated hsa-miR-328. Circ-AXL may serve as a potential therapeutic target for AD.	Circ-AXL promotes Abeta25-35-induced apoptosis, differentiation, and neuronal injury in SK-N-SH and SK-N-SI cells, and volatile stress in SK-N-SH cells. Circ-AXL may serve as a potential therapeutic target for AD.	Circ-AXL may serve as a potential therapeutic target for AD.	14911771
hsa_circ_AXL	Not available	Circ-AXL	AXL	hsa-miR-1306-5p	qPCR	Uterus (cell)	Cell lines (SK-N-SH, SK-N-SI)	14911771	Not available	Circ-AXL overexpression increased neuronal cell apoptosis, differentiation, and injury under Abeta25-35 stimulation. Circ-AXL negatively regulated hsa-miR-1306-5p. Circ-AXL may serve as a potential therapeutic target for AD.	Circ-AXL promotes Abeta25-35-induced apoptosis, differentiation, and neuronal injury in SK-N-SH and SK-N-SI cells, and volatile stress in SK-N-SH cells. Circ-AXL may serve as a potential therapeutic target for AD.	Circ-AXL may serve as a potential therapeutic target for AD.	14911771



These findings exemplify the importance of unraveling the circRNA-miRNA-target gene regulatory axes to provide a better understanding of the biological mechanisms implicated in AD, suggesting hsa_circ_LPAR1 and hsa_circ_AXL as the most promising circRNAs to be experimentally validated as biomarkers in this clinical context.

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