REVISTA NEUROCIÊNCIAS

Molecular interactions of long non-coding RNAs in hepatic encephalopathy associated with cirrhosis: a systematic review

Interações moleculares dos RNAs longos não codificantes na encefalopatia hepática associada à cirrose: uma revisão sistemática

Interacciones moleculares de los ARN largos no codificantes en la encefalopatía hepática asociada a la cirrosis: una revisión sistemática

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Resumo

Introdução. A encefalopatia hepática (EH) é uma síndrome neurológica complexa e potencialmente reversível, decorrente de doenças hepáticas agudas ou crônicas, caracterizada por alterações neuropsiquiátricas, cognitivas, motoras e de coordenação neuromuscular. Os estudos sobre o papel dos RNAs longos não codificantes (lncRNAs) na encefalopatia ainda são limitados. Portanto, está revisão sistemática descreve o papel dos lncRNAs nas diferentes vias de sinalização envolvidas na EH em pacientes cirróticos. **Método.** As bases de dados PubMed, Web of Science e LILACS foram utilizadas para identificar os estudos. Foram incluídos estudos com camundongos e/ou pacientes cirróticos com EH que avaliavam a expressão de lncRNAs e seus mecanismos de interação. **Resultados.** Dos seis estudos incluídos, 11 lncRNAs foram associados à EH (SIX3OS, lnc240, AL137857.1, lnc-FAM84B-8, lnc-SAMD3-1, ZFAS1, GAS5, uc007pjf.1, ENSMUST00000167589, uc007hha.1, ENSMUST00000124047). Três estudos foram realizados com pacientes cirróticos com EH, enquanto outros três utilizaram camundongos. Os resultados variaram entre expressão e silenciamento associados a mecanismos regulatórios. Na rede de interação entre as vias lnc240/miR-1264-5p/MEF2C, foi indicado que o lnc240 pode regular a expressão do MEF2C por meio do miR-1264-5p, afetando a plasticidade sináptica hipocampal. O silenciamento de SIX3OS1 aumentou a expressão de miR-743b-3p, reduziu os níveis de AQP1 e atenuou o desenvolvimento anormal de espinhas dendríticas induzido pela hiperamonemia, reforçando a relevância dessa interação. **Conclusão.** Esta é a primeira revisão sistemática a avaliar o papel dos lncRNAs e de suas

redes de interação na EH em pacientes cirróticos. Diversos lncRNAs regulam vias sendo expressos ou silenciados, influenciando miRNAs e mRNAs.
Unitermos. Encefalopatia hepática; lncRNA; miRNA; mRNA; lncRNA-miRNA-mRNA

Abstract

Introduction. Hepatic encephalopathy (HE) is a complex and potentially reversible neurological syndrome resulting from acute or chronic liver diseases, characterized by neuropsychiatric, cognitive, motor, and neuromuscular coordination alterations. Studies on the role of long non-coding RNAs (lncRNAs) in encephalopathy are still limited. Therefore, this systematic review describes the role of lncRNAs in the different signaling pathways involved in HE in cirrhotic patients. **Method.** The PubMed, Web of Science, and LILACS databases were used to identify studies. Studies with mice and/or cirrhotic patients with HE that evaluated the expression of lncRNAs and their interaction mechanisms were included. **Results.** Of the six included studies, 11 lncRNAs were associated with HE (SIX3OS, lnc240, AL137857.1, lnc-FAM84B-8, lnc-SAMD3-1, ZFAS1, GAS5, uc007pjf.1, ENSMUST00000167589, uc007hha.1, ENSMUST00000124047). Three studies were conducted with cirrhotic patients with HE, while three others used mice. The results varied between expression and silencing associated with regulatory mechanisms. In the interaction network between the lnc240/miR-1264-5p/MEF2C pathways, it was indicated that lnc240 can regulate MEF2C expression via miR-1264-5p, affecting hippocampal synaptic plasticity. Silencing of SIX3OS1 increased miR-743b-3p expression, reduced AQP1 levels, and attenuated hyperammonemia-induced abnormal dendritic spine development, reinforcing the relevance of this interaction. **Conclusion.** This is the first systematic review to evaluate the role of lncRNAs and their interaction networks in HE in cirrhotic patients. Several lncRNAs regulate pathways by being expressed or silenced, influencing miRNAs and mRNAs.
Keywords. Hepatic encephalopathy; lncRNA; miRNA; mRNA; lncRNA-miRNA-mRNA

Resumen

Introducción. La encefalopatía hepática (EH) es un síndrome neurológico complejo y potencialmente reversible, resultante de enfermedades hepáticas agudas o crónicas, que se caracteriza por alteraciones neuropsiquiátricas, cognitivas, motoras y de coordinación neuromuscular. Los estudios sobre el papel de los ARN largos no codificantes (ARNlnc) en la encefalopatía son aún limitados. Por lo tanto, esta revisión sistemática describe el papel de los ARNlnc en las diferentes vías de señalización implicadas en la EH en pacientes cirróticos. **Método.** Se utilizaron las bases de datos PubMed, Web of Science y LILACS para identificar estudios. Se incluyeron estudios con ratones y/o pacientes cirróticos con EH que evaluaron la expresión de ARNlnc y sus mecanismos de interacción. **Resultados.** De los seis estudios incluidos, 11 lncRNAs se asociaron con EH (SIX3OS, lnc240, AL137857.1, lnc-FAM84B-8, lnc-SAMD3-1, ZFAS1, GAS5, uc007pjf.1, ENSMUST00000167589, uc007hha.1, ENSMUST00000124047). Tres estudios se realizaron con pacientes cirróticos con EH, mientras que otros tres utilizaron ratones. Los resultados variaron entre la expresión y el silenciamiento asociado con los mecanismos reguladores. En la red de interacción entre las vías lnc240/miR-1264-5p/MEF2C, se indicó que lnc240 puede regular la expresión de MEF2C a través de miR-1264-5p, afectando la plasticidad sináptica hipocampal. El silenciamiento de SIX3OS1 aumentó la expresión de miR-743b-3p, redujo los niveles de AQP1 y atenuó el desarrollo anormal de las espinas dendríticas inducido por la hiperamonemia, lo que refuerza la relevancia de esta interacción. **Conclusión.** Esta es la primera revisión sistemática que evalúa el papel de los lncRNA y sus redes de interacción en la EH en pacientes cirróticos. Varios lncRNA regulan vías de expresión o silenciamiento, lo que influye en los miRNA y los mRNA.
Palabras clave. Encefalopatía hepática; lncRNA; miRNA; mRNA; lncRNA-miRNA-mRNA

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INTRODUCTION

Hepatic encephalopathy (HE) or portosystemic encephalopathy is a complex, largely reversible neurological syndrome that occurs in patients with acute or chronic liver failure, or when portosystemic shunts bypass the liver[1]. First described in 1793 by John Abernethy, portosystemic shunt is a rare condition and consists of a congenital vascular anomaly, in which blood from the portal vein drains directly into a systemic vein, bypassing the hepatic circulation[2,3]. HE is a common consequence of advanced-stage liver disease that can result from multiple causes, such as liver failure, hepatitis and cirrhosis[4]. HE presents multifaceted clinical manifestations, including varying degrees of attention deficit, cognitive impairment, and psychomotor abnormalities, with patients' quality of life and prognosis being seriously affected, with morbidity tending to increase annually[5,6].

Normal brain function requires the anatomical integrity of the brain, through the production of sufficient energy and the efficiency of synaptic neurotransmission, however, in HE this ends up being impaired[7,8]. Even though the mechanism of this deficiency is not very clear, several factors and pathways interact with each other, resulting in dysfunction of the Central Nervous System (CNS), which manifests clinically as varying degrees of HE[7,8]. It is known that systemic inflammation, neuroinflammation, as well as cellular senescence and oxidative stress are implicated in the disease[9]. It is understood that in acute liver failure, cerebral

hyperammonemia causes morphological changes in astrocytes with the production of glutamine, leading to osmotic stress, in addition to the development of cytotoxic cerebral edema, being one of the main drivers of cognitive impairment in HE[10,11]. Other morphological changes present in patients with chronic liver disease with Alzheimer's astrocytosis type II, showed a large swollen nucleus, prominent nucleolus and margination of the chromatin pattern[12]. During the HE process, cytokines cannot cross the blood-brain barrier (BBB), however, it is known that the peripheral immune system can still signal the brain, provoking a response against inflammation, expressing pro-inflammatory cytokines, such as IL- 1β, IL-6 and TNF-α, in the periphery and the brain, through active transport[13]. A study carried out with HE models in rats, for example, showed that with the increase in ammonia contraction, the release of pro-inflammatory molecules, such as IL-1β and IL-6, occurred and consequently caused the modification of the expression of GABAa and GluRI, disruption of the BBB, promotion of microgliosis-like deterioration of learning and spatial memory in the hippocampus of these mice[14,15].

In addition to BBB permeability/function, cerebrospinal fluid composition, glymphatic flow, cerebral energy metabolism, neurotransmission, and cell-to-cell communication are all disturbed, causing neurological impairment and providing potential therapeutic targets[9,16]. It is believed that, in addition to cleaning the brain, the glymphatic system contributes to the distribution of growth

factors, neuromodulators, transport proteins and other solutes within the brain and that its failure can have consequences[17]. Recently, a study analyzed frontal brain regions, the olfactory bulb and the prefrontal cortex, of BDL rats (hepatic cirrhosis induced by bile duct ligation) and indicated a relationship in the dysfunction of the glymphatic clearance system in HE, reinforcing this hypothesis[18]. Currently, several potential therapeutic targets are studied, which may include the antagonism of pro-inflammatory cytokines[19], antioxidants like N-acetylcysteine[20], albumin[21], probiotics[22], hypothermia[23], rifaximin[24] e indomethacin[25].

It is understood that it is associated with liver failure[26]. However, there are underlying causes that contribute to the development of liver disease, such as alcohol abuse, obesity and viral hepatitis (particularly hepatitis C), sarcopenia[27], altered intestinal microbiota[28], circulatory disorders, nutritional deficits[29], in addition to extrahepatic conditions, such as diabetes and aging[26]. Currently, HE is classified into three subtypes: Type A develops as a result of alcoholic liver disease (ALF) and is associated with osmotic disorders in the brain, systemic inflammation and high intracranial pressure, which can cause brain hernia[30]. Types B and C, although they share similar pathophysiology, have different prognoses[31]. In type B, HE is associated with portosystemic bypass or shunt in the absence of intrinsic liver dysfunction and type C is caused by cirrhosis, the most common risk factor for HE, leading to hospitalizations and repeated readmissions[31,32]. Within type C, there are several different forms, including

covert, persistent and episodic[33]. Episodic encephalopathy varies in severity and duration, recurrent encephalopathy is defined as more than two episodes in a year, and persistent encephalopathy is defined as cognitive impairment that limits activities of daily living for a period of more than two weeks[33]. Most of the changes observed in the three types of encephalopathy are promoted by the repression or expression of genes by ncRNAs, especially miRNAs and lncRNAs[34,35].

Long non-coding RNA (lncRNA) is a key component of the transcriptome over 200 nucleotides long[36]. In addition to limiting the protein-coding potential, it plays an important role in several neurological diseases[37], like Alzheimer's disease[38] and Parkinson disease[39]. It also participates in liver diseases, such as cancer[40]. These lncRNAs do not code for proteins, however, their action targets interference in genetic transcription involving inflammation, apoptosis and oxidative stress[36] lncRNAs are classified mainly according to their location in the genome compared to their closest protein-coding genes, being intergenic (interspersed between coding regions) or intragenic (located within or very close to the coding genes in sense or antisense orientation)[41]. lncRNAs can also be classified from a functional perspective as trans-acting (functioning in a similar way to proteins and located in cellular regions distant from the lncRNA transcription site) or cis acting (controlling the expression of neighboring genes through transcriptional interference or chromatin modifications)[41]**.** Often, through

complex three-dimensional interactions and configurations, lncRNAs bind to DNA, RNA and proteins, participating in an immense range of biological activities, such as modulating gene expression[42], recruitment of histone modifiers to chromatin[43], pluripotency, cell differentiation[44] and regulation of alternative splicing[45].

It is understood that learning and memory dysfunction in HE mice may be due to reduced density and maturity of hippocampal neuronal dendritic spines and studies have demonstrated that the normal morphology of dendritic spines is important for cognitive function, being critical for learning. and memory in patients with AD[46,47]. Recent studies have examined HE brain lncRNAs associated with acute liver failure and found that these lncRNAs are mainly involved in inflammation and neuropathology[35]. Most ncRNAs, such as lncRNAs and microRNAs, are transcribed by RNA polymerase II and use the same consensus splicing signals as protein-coding genes, being post-transcriptionally modified at the 5' and 3' ends[48]. Several publications have reported correlation of lncRNA-mediated regulation of gene expression through the miRNA sponge, however, in general, levels of lncRNAs need to be abundant enough to mediate miRNA repression[49]**.** MicroRNAs (miRs), a group of small non-coding and evolutionarily conserved RNAs (18 to 24 nucleotides in length), are known to contribute importantly to the control of thousands of downstream genes by regulating genetic transcription[50,51]. miRs have gained enormous interest in the field of biomarker research, and evidence confirms their

involvement in liver aging, the pathogenesis of liver diseases, and transplantation[52]. The expression of several miRNAs changes in the brain and during the development of alcoholic liver disease (ALF), with many of the altered miRNAs targeting mRNAs that control cellular and molecular mechanisms essential for the homeostatic function of the brain[53].

The explanation of the mechanism in the formation of diseases can be elucidated through a variety of lncRNAs with special structure or consistent sequence, which regulate gene expression through different basic routes through interaction with different molecules, including miRNA and mRNA[54,55]. In central nervous system (CNS) diseases, ncRNAs play significant gene regulatory roles, coordinating many biological functions[56]. Genetic microarrays provide a large amount of analyzable data, which has made them widely used in brain disorders[57]. Currently, numerous multiomic databases of brain metabolism exist, including Minimal Hepatic Encephalopathy (MHE)[58]. Several biological samples of brain tissue, serum and other body fluids have already been detected, allowing the modeling of a highly complex metabolic network and the identification of specific characteristics of HE[58,59].

Knowing this, this systematic review compiled studies that examined the roles of lncRNAs in different signaling pathways in hepatic encephalopathy in cirrhotic patients, identifying potential therapeutic targets.

METHOD

This review mainly focused on identifying the expression or repression of different lncRNAs (non-coding RNAs) and their regulatory mechanisms in Hepatic Encephalopathy (HE) in cirrhotic patients.

This study used the "Preferred Reporting for Systematic Reviews and Meta-analysis" guidelines.

Database and search strategies

The selection of studies was carried out from the PubMed (NCBI), Web of Science (WoS) and Latin American and Caribbean Health Sciences Literature (LILACS) databases. The following search terms (search strategy) were used: ''lncRNA AND hepatic encephalopathy, miRNA AND hepatic encephalopathy, Mrna AND hepatic encephalopathy, lncRNA-miRNA-mRNA AND hepatic encephalopathy''. The Boolean search term AND was used to define the search. The studies were systematically selected through articles related to lncRNA and its role in HE in cirrhotic patients. Research articles with results available to readers written in English were considered. Searches across all databases were grouped and duplicate references removed.

Inclusion criteria

The inclusion criteria were as follows: i) Research studies in mice or cirrhotic patients with hepatic encephalopathy, specifically reporting the expression levels

of lncRNAs and their interaction mechanisms; and ii) studies with relevant data on the association between Hepatic Encephalopathy and lncRNAs, in the English language.

Exclusion criteria

The exclusion criteria were as follows: i) studies that did not include as their focus the expression of lncRNAs correlated with Hepatic Encephalopathy; ii) studies with incomplete data, review articles, case reports, reviews, books, conference abstracts, and other non-original research publications.

Study selection and data extraction

Two reviewers (LBC and ACC) independently analyzed the databases, using the titles and abstracts identified that met the eligibility criteria. Subsequently, with the assistance of a third reviewer (LMDS), the initial disagreements between the first two reviewers were resolved. Articles that did not meet the inclusion criteria and the reasons for exclusion were recorded. Subsequently, the following data were extracted from each selected study: Author, Year, selected lncRNAs, regulation mechanism, results obtained and conclusion.

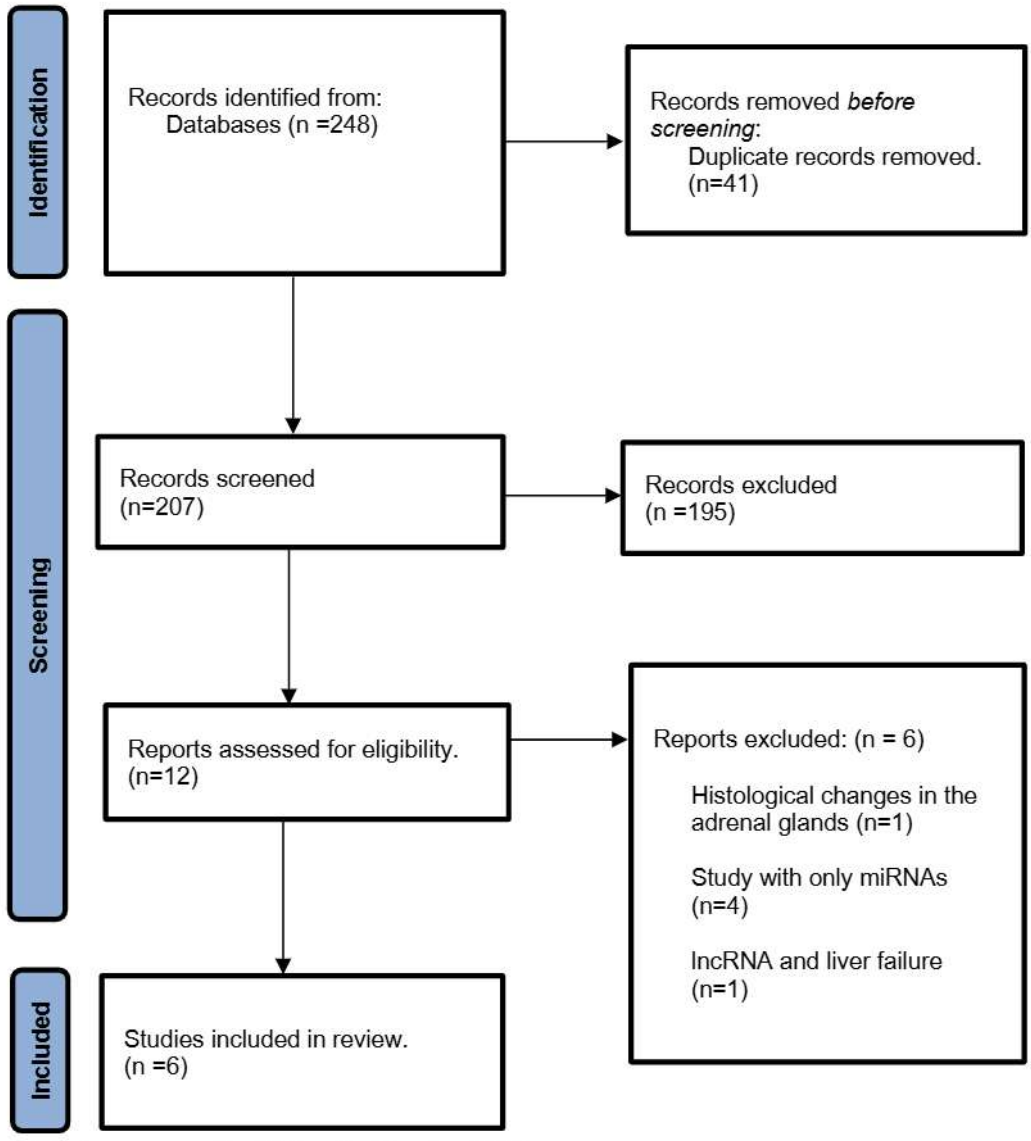
RESULTS

Search results

In total, 248 articles were initially identified in the databases consulted. After removing duplicates, 207 articles

remained. In the first phase, after evaluating the titles and abstracts, 195 articles that did not meet the objective of the review were excluded. In the second phase, the chosen articles were read in full, totaling 12 articles. Subsequently, six articles were excluded. In the end, six publications were included in this review. Details of identification, screening and included studies are shown in Figure 1.

Figure 1. The study selection process.



lncRNA, long non-coding RNA. miRNA, microRNAS

Study characteristics

Two studies by Zhang 2022[60] and Zhang 2023[61], detected lncRNAs by RNA-seq. In the first study[60] identified 229 significantly altered lncRNAs in the hippocampus of mice with HE, including 116 downregulated and 113 upregulated transcripts, showing a balanced distribution between both directions. Three lncRNAs were selected for validation using quantitative real-time PCR (qRT-PCR), and the results were consistent with the RNA-seq data, supporting the reliability of the findings. Three lncRNAs were selected for qRT-PCR analysis, being consistent with the RNA-seq data, indicating reliability in the results, and based on the lncRNA-miRNA-mRNA interaction networks, in HE mice, a total of 73 lncRNAs had interactions with 39 miRNAs and 134 mRNA, with lncRNAs and mRNAs being targets of miRNAs[60]. The production of ceRNA networks contained five main miRNA nodes (miR-743b-3p, miR-376c-5p, miR-708-y, mmu-miR-1264-5p, miR-34b-5p), with lncRNAs (Fos, Jade2 and Npas4) were target genes of miRNA-34b-5p, while Aqp1 was the target gene of miR-743b-3p[60]. SIX3OS1 was one of the lncRNAs selected in the ceRNA network, being significantly upregulated[60]. In the second study, lnc240 was detected downregulated in the hippocampus of HE mice, and in addition to it, other lncRNAs showed significant differences, such as Nrp2, Lrp4, Brix1, Spata6, Slc38a10[61]. Also, an interaction network between the lnc240/miR-1264-5p/MEF2C pathways was predicted, and as a result, in vitro experiments, and later in vivo, indicated that lnc240 can

regulate MEF2C expression through miR- 1264-5p and therefore affect changes in hippocampal synaptic plasticity[61].

Zhang 2022[62] identified a total of 44 pairs of lncRNA-mRNA interactions, which included 16 lncRNAs and 41 mRNAs(62). AL137857.1 had the most interactions with downstream mRNAs, including AIF1, used as a marker of microglial cells[62]. Wang 2021[63] analyzed the microarray dataset of 11 cirrhotic patients, 6 with EHM and 5 without EHM. lncRNA-mRNA expression identified a total of 64 diff-lncRNAs, of which 30 lncRNAs were upregulated while the rest were downregulated[63]. In another study, the transcription of protein-coding and non-coding RNAs was evaluated through RNA sequencing analysis, applying a rigorous set of identification criteria, in which lncRNAs were associated with hepatic encephalopathy in brain tissues of BDL mice (murine bile duct ligation model)[64]. In total, eight lncRNAs were differentially expressed and probably associated with HE, including GAS5 and ZFAS1, with GAS5 being transcribed in the opposite direction to its neighbor, Zbtb37, while Zfas1 was transcribed antisense to its neighboring gene Znfx1, both in mice and humans[64].

To understand which lncRNAs are involved in brain dysfunction in ALF, a study was carried out with an experimental mouse model versus a control group simulated by microarrays[35]. Of these, 382 lncRNAs were upregulated and 486 lncRNAs were downregulated[35]. Fourteen pathways corresponding to lncRNAs were positively regulated, in which 10 pathways showed highly significant regulation, including:

ENSMUST00000130314, AK089350, ENSMUST00000147219, ENSMUST00000120139, uc007hha.1, uc007pjf.1, AK134032, mki.1, ENSMUST00000137657 and NR_015470[35]. The characteristics, results and conclusions of the included studies are presented in Table 1, Figure 2, and Figure 3.

DISCUSSION

As far as we know, Central Nervous System (CNS) dysfunction has been clinically manifested to varying degrees in HE, in addition, long non-coding RNAs (lncRNA) have played an important role in this, as well as in several neurological diseases[7,8,37]. With the increase in genetic microarrays in brain disorders, including minimal hepatic encephalopathy, a more in-depth study of lncRNAs and their regulatory pathways has become necessary[57–59]. Therefore, this systematic review aimed to identify and describe studies evaluating the profile of HE lncRNAs in cirrhotic patients and their regulatory mechanisms, mainly in miRNAs and mRNAs.

A recent study analyzed the expression profiles of lncRNAs, miRNAs and mRNAs in the hippocampus tissues of normal mice and mice with HE, by RNA-seq, and the constructed interaction networks pointed to Aquaporin 1 (AQP1), as one of the most important genes. significant, and its silencing attenuated cognitive impairment in AD through activation of the Wnt signaling pathway[60].

Table 1. Study of the main lncRNA, their regulatory mechanisms and conclusion.

Autor	lncRNA	Mecanismo de regulação	Resultados	Conclusão
Zhang *et al.* 2022[60]	SIX3OS1	miR-743b-3p/ AQP1	In the ceRNA network, SIX3OS1 is upregulated, confirming the silencing of SIX3OS1. SIX3OS1-shRNA cells showed that SIX3OS1 upregulated the expression of its target miR-743b-3p, whereas AQP1, EBF2, NKAIN3, and ISL1 were downregulated. When treated with NH4Cl, SIX3OS1 silencing improved dendritic spine maturity and synaptic function.	SIX3OS1 silencing upregulated the expression level of miR-743b-3p and decreased the expression level of AQP1.
Zhang *et al.* 2023[61]	lnc240	miR-1264-5p/ MEF2C	Overexpression of lnc240 led to a significant decrease in the expression of miR-1264-5p, in addition, inhibition of miR-1264-5p could increase the expression of MEF2C in neurons treated with NH4Cl. As a result, lnc240 showed improvements in the morphology and synaptic function of neurons in the hippocampus of mice.	Overexpression of lnc240 increased its binding of miR-1264-5p, increasing the expression level of MEF2C.
Zhang *et al.* 2022[62]	AL137857.1	AIF1	AL137857.1 expression was upregulated in HE patient samples. Among its interactions, AL137857.1 had the highest number of interactions with downstream mRNAs, AIF1. The lncRNA AL137857.1 was gradually upregulated, prolonging its expression level with an increasing LPS treatment period.	AL137857.1 had the highest number of interactions with downstream mRNAs, such as AIF1, a marker widely used in microglial cells.
Wang *et al.* 2021[63]	lnc-FAM84B-8 lnc-SAMD3-1	Regulation mechanisms of lnc-FAM84B-8: CXCR3 – CXCR6 Regulation mechanisms of lnc-SAMD3-1: EOMES – STATI – CXCR3 – CD8A – CCR5 – CCL5	lnc-FAM84B-8 and lnc-SAMD3-1 were identified as core lncRNAs, being closely related to the core mRNA network. The expression of lnc-FAM84B-8 was upregulated in HE, while lnc-SAMD3-1 was downregulated when patients progressed to, HE.	The expression of lnc-FAM84B-8 was upregulated in HE, while lnc-SAMD3-1 was downregulated when patients progressed to HE.
Cheon *et al.* 2022[64]	ZFAS1 GAS5	Regulation mechanisms of ZFAS1: Znfx1 Regulation mechanisms of GAS5: Zbtb37	The expression profile of the cortex tissues of a BDL model that during hyperammonemia, ZFAS1 and GAS5 were expressed. GAS5 was transcribed in the opposite direction to its neighboring gene, Zbtb37, in both mice and humans, whereas Zfas1 was the antisense transcript to its neighboring gene Znfx1 in mice and humans. The increase in intracellular ammonia level decreased due to the silencing of ZFAS1 or GAS5, which also occurred in supernatant samples.	ZFAS1 and GAS5 are implicated in the apoptosis of cultured neuronal cells, and in the modulation of extracellular and intracellular ammonium levels, contributing to hyperammonemia-induced neuronal injury and cell death.
Silva *et al.* 2017[35]	uc007pjf.1 ENSMUST00000167589 uc007hha.1 ENSMUST00000124047	Regulation mechanisms of uc007pjf.1 and ENSMUST00000167589: NET1 e genes Rrp7a Regulation mechanisms of uc007hha.1 and ENSMUST00000124047: Slc16a7 e genes Acsl6	lncRNAs are involved in the control of the MAPK pathway in ALF, possibly in conjunction with miRNAs. It was observed that ALF-responsive lncRNAs were also involved in controlling the insulin signaling pathway, which plays an important role in maintaining glucose homeostasis.	uc007pjf.1 and ENSMUST00000167589 are associated with the neuroepithelial transformation gene 1 (NET1) and the Rrp7a and uc007hha.1 genes, and ENSMUST00000124047 was associated with the Slc16a7 and the Acsl6 genes, respectively.

Figure 2. Disease stages (hepatic encephalopathy and minimal hepatic encephalopathy), types of samples (mice or humans) and lncRNAs studied in the articles. The stages of HE was presented in different studies, with both hepatic encephalopathy and minimal hepatic encephalopathy being found, in addition to the types of samples (murine or human model) and the most important lncRNAs that were studied.

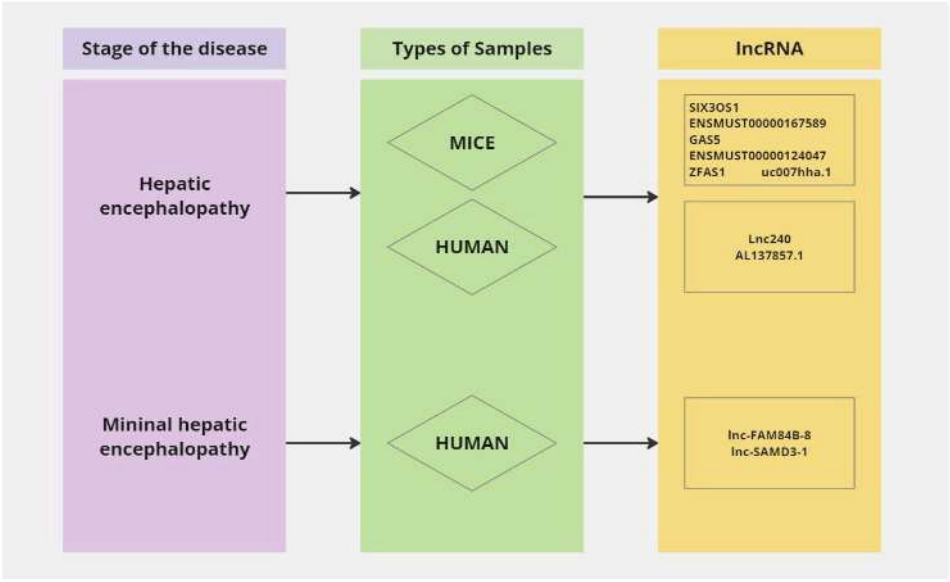
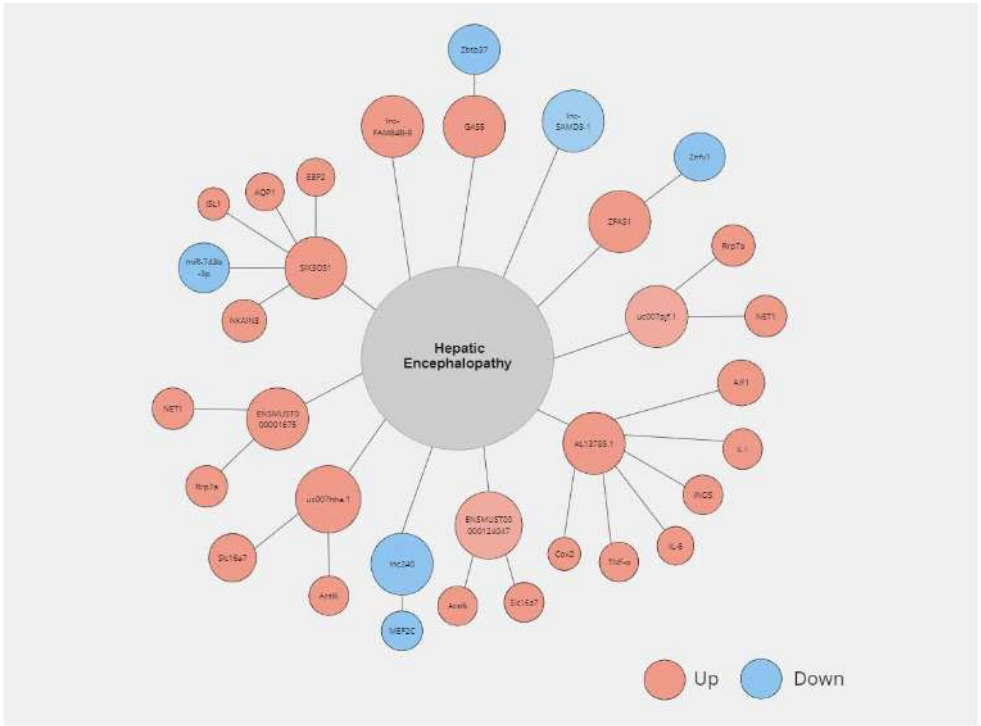


Figure 3. LncRNAs expressed in Hepatic Encephalopathy. In most studies, lncRNAs were positively regulated during HE, on the other hand, lnc240 and lnc-SAMD3-1 were negatively regulated. Lnc240 negatively regulated MEF2C, being repressed as a result of its interaction with miR-1264-5p, directly affecting the maturity of dendritic spines, density and synaptic dysfunction. SIX3OS1 is negatively regulated, positively regulating the expression level of miR-743b-3p. ZFAS1 and GAS5 were positively regulated, while their neighboring genes, ZBTB37 and ZNFX1, were negatively regulated, which may have a regulatory relationship. Lnc-FAM84B-8 was upregulated in HE, whereas lnc-SAMD3-1 was downregulated.



Aquaporins (AQPs) are a family of small integral transmembrane proteins present in a variety of subcellular membranes of prokaryotic and eukaryotic cells, forming water channels[65,66]. AQPs, in neurological conditions, have been proposed as potential therapeutic targets in inflammatory neuronal diseases, with reported changes in human brains affected by various neurodegenerative disorders. Therefore, their silencing may contribute to the protective effect and thus improve cognitive function of neurodegenerative diseases such as AD[66–68].

In the results of Zhang 2022[60], SIX3OS1 silencing upregulated the expression level of miR-743b-3p and decreased the expression level of AQP1, improving the abnormal development of dendritic spines caused by hyperammonemia, also corrected the disorder of synaptic neurotransmission, reinforcing the importance of the interaction of lncRNAs-miRNAs in the regulation of mRNA expression, playing important roles in the development of the nervous system, transmission and synaptic organization of HE mice. SIX3OS is co-expressed with the homeodomain factor Six3, a homolog of the Drosophila sine oculis gene[69]. Its knockdown results in deficits in lineage specification through the modulation of SIX3 activity, in addition to acting as a molecular scaffold recruiting histone-modifying enzymes to target genes of the homeodomain factor Six3, which can regulate the activity of protein-coding genes that play a role vital role in controlling neurodevelopment[50,51]. Recently, a

study showed that upregulation of SIX3OS1 was able to attenuate oxidative stress in neurons in mice induced by CUMS (chronic unpredictable mild stress), in behaviors like depression[70]. Furthermore, Zou, Tianyu et al. 2024, revealed that the functional mechanism of ZZCD (Zhi-zi-chi decoction - a traditional Chinese medicine formula that exerts antidepressant effects that suppresses depressive behaviors in CUMS-induced rats) through the Six3os1/BDNF axis provided new clues in prevention and treatment of depression, with SIX3OS1 increasing the expression of BDNF (brain-derived neutrophic factor) mediating the modification of histone H3K4 methylation of the BDNF promoter[71,72]. As a result, Zhang 2022[60] raised the hypothesis that learning and memory dysfunction can be regulated through the lncRNA SIX3OS1 in the expression of AQP1 through the targeted binding of miR-743b-3p, highlighting the importance of further studies regarding specific regulatory mechanisms.

In the second study by Zhang 2023[61], found that lnc240 expression was downregulated in the hippocampus of HE mice, which resulted in a decrease in lnc240 bound to miR-1264-5p in addition to an increase in miR-1264-5p bound MEF2C, leading to repression of MEF2C, which directly affected the maturity of dendritic spines, density and synaptic dysfunction. MEF2C (myocyte-specific enhancer factor 2c) is essential for the development of neuronal cells, such as in the postsynaptic differentiation of dendrites, regulating the number of excitatory synapses[53]. Furthermore, it has important functions in IFN-I-dependent

inflammatory responses and B cell proliferation[73–77]. This same study also pointed out that overexpression of lnc240 in an environment with high ammonia content led to an increase in the expression levels of lnc240 and MEF2C, decreasing the level of miR-1264-5p, and concluded that overexpression of lnc240 in vitro, can help improve synaptic function, rescuing spatial memory and learning dysfunction in mice[61]. Highly expressed in the hippocampus, cortex, amygdala and other brain regions related to learning and memory, MEF2C is involved in angiogenesis, bone development, muscle cell differentiation, cardiac morphogenesis and development of the lymphatic system, in addition to being involved in the growth and pruning of dendrites of the neuronal axis[78–82]. In neural networks, MEF2C maintains balance, regulating the inhibitory and excitatory states of neurons, and conditional MEF2C knockout mice confirmed its involvement in the migration of GABA and glutamate pyramidal neurons, as well as in the maintenance of synaptic stability and function[83,84]. Corroborating the in vitro study, the in vivo study was also performed, demonstrating that overexpression of lnc240 can improve MEF2C expression levels, increasing the density and maturity of dendritic spines in HE mice[61].

In the lncRNA-mRNA interaction network, from the study by Zhang 2022[62], lncRNA AL137857.1 was located in a central position with the most regulatory mRNAs downstream, as is the case with AIF1. Several studies associate AIF1 with inflammation and immunoinflammatory

diseases, such as cancer, in addition to promoting the activation of macrophages and the growth of T lymphocytes. Therefore, the AIF1 protein can function as a biomarker and therapeutic target, for example, in several pathological inflammatory processes including autoimmune lesions and allograft rejection[85–88]. AIF1-positive gliocytes were associated with a poor prognosis in cerebral astrocytoma, furthermore, it is suggested that AIF1 promoted liver cancer progression by increasing M2 polarization and increasing CXCL16 secretion in macrophages[89,90]. AL137857.1 has proven to be a downstream regulator of inflammatory cytokines, with activation of microglial cells being implicated as a factor in inflammation in the brain, followed by the release of several pro-inflammatory cytokines, including TNF-α, IL-1β and IL -6, in addition to the phagocytosis capacity of microglia, impaired when treated with siRNA AL137857.1[62]. Even with some limitations such as the lack of in vivo experiments and the microarray data being from patients with different health conditions and severities, this study pointed out for the first time the biological role of the lncRNA–mRNA network in the transition from normal to cirrhosis and for HE, targeting AL137857.1 as a possible future therapeutic strategy for HE[62].

A study in patients with MHE related to cirrhosis identified an interactive network of lncRNAs-mRNAs, in which lnc-FAM84B-8 and lnc-SAMD3-1 were analyzed, concluding that they were up/down regulated separately[63]. Furthermore, an enrichment analysis indicated an

association in the regulation of genes associated with inflammation, innate and adaptive immune responses[63]. Previous studies have examined the relationship between HE associated with acute liver failure and brain lncRNAs, and as a result, found that lncRNAs are mainly involved in inflammation and neuropathology[91]. The immune system occupies central status in cirrhotic patients with MHE, this was done through a peripheral gene expression network[92]. Among the various upregulated cytokines, CCL20, CX3CL1, CXCL13, IL-15, IL-22 and IL-6 were identified, involved in 3 pathways related to the immune system, such as the "adaptive immune response", "immune response'' and "chemotaxis"[92]. Therefore, this study showed the relationship between the regulatory functions of lncRNAs in the MHE and immunological inflammatory processes, therefore, lncRNAs can be a crucial component in this process through their immunoregulatory functions[63].

Through a BDL model, mice were induced to liver failure, simulating hyperammonemia and as a result, the simulation caused hepatic encephalopathy, demonstrating an increase in the level of ammonia, cell death, neuronal damage in the cerebral cortex, in addition to several lncRNA candidates that showed differential expression in the brains of normal and BDL mice[64]. It is known that hyperammonemia impairs synaptic plasticity, and is involved in corticostriatal and hippocampal pathways, affecting learning behavior[93]. In this study, transcribed lncRNAs (ZFAS1 and GAS5) were revealed to be implicated in extracellular and intracellular

modulation of ammonia levels and apoptosis in neuronal cell culture[64]. ZFAS1 participates in the pathogenesis of several human diseases, mainly exerting its effect through the miRNA sponge, as is the case of miR-589, miR-7–5p and miR-892b[94]. A recent study demonstrated that ZFAS1 is associated with the malignant status and prognosis of patients with hepatocellular carcinoma through the ZFAS1/miR-150-5p axis, while another study demonstrated that overexpression of GAS5 promoted the apoptosis of hepatoma cells[95,96]. In HCC (Hepatocellular Carcinoma) tissues and cell lines, ZFAS1 was found to be significantly downregulated, while its overexpression inhibited proliferation and induced cell apoptosis in HCC cell lines, suggesting it as a new prognostic biomarker and target for clinical treatment of CHC[97]. In the case of GAS5, its participation in signaling pathways can occur in three ways: firstly as a signaling protein, being specifically transcribed following different triggers and participating in signal transmission in various pathways as a signaling node, secondly as a decoy, behaving as a molecular sponge, binding directly to RNA or target proteins and blocking subsequent functions or thirdly as a guide where it can bind and guide the protein to a specific DNA sequence, being able to regulate the transcription of downstream molecules[98–100]. Through RNA sequencing data, the study found that the neighboring genes ZBTB37 and ZNFX1 did not undergo notable changes in terms of transcription level and that,

therefore, they may have a regulatory relationship with ZFAS1 and GAS5[64].

Silva 2017[35] found in their studies that lncRNAs are involved in controlling the MAPK pathway in ALF, possibly in conjunction with miRNAs. It was also demonstrated that activation of the MAPK pathways boosted the expression of COX-e contributing to microglia-induced neuronal cell death, therefore, the activation of signals that diverge from the MAPK pathways may act as critical mediators of neuroinflammation and play important roles in diseases. neurodegenerative (86,87). In this study, 9 lncRNAs with altered expression were identified, all positively regulated, of which four were associated with previously identified genes (NET1, Slc16a7, Acsl6 and Rrp7a)[35]. It has already been demonstrated that overexpression or reduction of NET1 could induce or suppress the proliferation, migration, and invasion of HCC cells, in addition to playing a mediating role in the tumorigenesis and metastasis of HCC in vivo[101].

CONCLUSION

In conclusion, this was the first systematic review that reported the role of lncRNAs and their interaction networks in Hepatic Encephalopathy in cirrhotic patients. It has been demonstrated that several lncRNAs can be expressed or silenced, acting as a mechanism for regulating other pathways, such as miRNAs and mRNAs. Among them, SIX3OS1 can act as a ceRNA of miR-743b-3p reaching AQP1, regulating synaptic function, and consequently, affecting

memory dysfunction induced by HE. However, more studies must be carried out to identify potential therapeutic targets and future research avenues for this field.

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