J Neurol Neurosci ©
13 (12) 2022 : 001-03 • MINI REVIEW

MicroRNA overexpression in men with lafora disease is age-related

Concepcion Aguado*
Department of Physiology, Facultat de Medicina i Odontologia, Universitat de València, 46010 Valencia, Spain

SUMMARY

Lafora complaint is a rare, fatal form of progressive myoclonus epilepsy characterized by nonstop neurodegeneration with epileptic seizures, characterized by the intracellular accumulation of aberrant polyglucosan grains called Lafora bodies. Several workshop have handed multitudinous substantiation of molecular and cellular differences in neural towel from experimental mouse models deficient in either laforin or malin, two proteins related to the complaint. Oxidative stress, differences in proteostasis, and deregulation of seditious signals are some of the molecular differences underpinning this condition in both KO beast models. Lafora bodies appear beforehand in the beast's life, but numerous of the forenamed molecular aberrant processes and the consequent neurological symptoms postdate only as creatures age. Then, using small RNA-seq and quantitative PCR on brain excerpts from laforin and malin KO manly mice of different periods, we show that two different microRNA species, miR- 155 and miR- 146a, are overexpressed in an age-dependent manner. We also observed altered expression of apparent target genes for each of the microRNAs studied in brain excerpts. These results open the path for a detailed analysis of the molecular consequences of laforin and malin insufficiency in brain towel, as well as the implicit part of miR- 155 and miR- 146a as specific biomarkers of complaint progression in LD.

Keywords: Epilepsy; microRNA; gene expression; Neuroinflammation

Address for correspondence:

Concepcion Aguado, Department of Physiology, Facultat de Medicina i Odontologia, Universitat de València, 46010 Valencia, Spain
E-mail: Aguado53@gmail.com

Word count: 356 **Tables:** 00 **Figures:** 00 **References:** 05

Received: 01.12.2022, Manuscript No. ipjnn-23-13379; **Editor assigned:** 03.12.2022, PreQC No. P-13379; **Reviewed:** 17.12.2022, QC No. Q-13379; Revised: 23.12.2022, Manuscript No. R-13379; **Published:** 31.12.2022

INTRODUCTION

Lafora complaint (LD) is a rare inheritable condition (OMIM254780, ORPHA# 501) caused by either mutations in the locus EPM2A, rendering for the binary particularity phosphatase laforin, or EPM2B, rendering for the E3 ubiquitin ligase malin. LD is a fatal progressive myoclonus epilepsy characterized by alcohol – clonic seizures, myoclonus, visual visions, ataxia, and madness, followed by a rapid-fire neurodegenerative progression that results in the death of cases with a median complaint duration of 11 timessince the onset of the first symptoms. There's no cure for this terrible complaint beyond palliative treatments; still, over the last many times, exploration has produced multitudinous molecular data that give accumulating substantiation of its pathophysiology. For case, the accumulation of aberrant glycogen intracellular deposits, called Lafora bodies (LBs), has attracted utmost of the focus in LD exploration, and constitutes the target of numerous therapeutical strategies proposed so far. still, molecular impairment of laforin and/ or malin, which work as a functional complex (involved in numerous molecular pathways not only related to glycogen metabolism but also to proteostasis pathways and the ubiquitin – proteasome system) leads to numerous cellular differences that feel independent of the progression of LBs accumulation and their consequences for neuronal survival.

LITERATURE REVIEW

Former studies have shown that utmost of the features of the pathological phenotype in LD mice models generally increase with age, corresponding complaint progression in humans; our former work proved that the neuroinflammatory geography in LD mice models becomes apparent, especially around 12 months of age. Grounded on these data, we sought o determine whether the observed increase in the expression situations for both microRNAs was also a late- onset event, related to this progressive seditious disbalance, or, on the other hand, a more primary one, near to the onset of the first symptoms. With this end, we compared the expression situations in brain excerpts from mice at 3, 7, 12, and 16 months of age. the expression situations start to come significantly advanced in 12- month-old Epm2b –/ – mice, and reach a outside at 16 months for both Epm2a –/ – and Epm2b –/ – mice.

We searched for miR- 146a and miR- 155 targets in miRTarbase; in parallel, we searched for miRNA – target

relations using the TargetScan (penetrated on 30 May 2018)) vaticination algorithm, and for targets of the corresponding microRNAs according to an expansive hunt of the being literature. From the combined results of these reciprocal quests, we named a set of apparent target genes to be farther validated, as follows Nsun3 and Socs1 for miR- 155; Glra2, Btg2, Traf6, and Sod2 for miR- 146a. Unexpectedly, not only did we not gain a significant drop in the expression situations of these genes (except for Btg2, which was slightly downregulated in Epm2a –/ – mice as compared to WT creatures), but we registered an increase in the gene expression situations of Nsun3 and Socs1 in both KO mice models, an increase in Glra2 in both KO mice models, and, eventually, an increase in Sod2 and Traf6 only for the Epm2b –/ – mice. Regarding Btg2, only a slight but significant drop in the expression situations was registered in the Epm2a –/ – mice. All the genes anatomized are ever related to molecular pathways applicable to the pathophysiological environment of LD Nsun3 (NOP2/ Sun RNA methyltransferase 3) encodes a mitochondrial methyltransferase related to encephalomyopathy and seizures(Glra2 (glycine receptor nascence 2) encodes for a glycine receptor that has been prognosticated to impact cognition, literacy, and memory in the developing brain; Btg2 (BTGanti-proliferation factor 2) is ananti-proliferative gene that, interestingly, has been supposed as a neuroprotective gene in mouse models of Huntington's complaint and Traf6(TNF receptor- associated factor 6) is an vulnerable response controller with an E3 ubiquitin ligase exertion that has been shown to interact with Sod1 in rat models of amyotrophic side sclerosis (ALS), promoting aggregatioin.

Noteworthy is the pronounced overexpression observed for the mitochondrial dismutase Sod2(superoxide dismutase 2) and Socs1 (suppressor of cytokine signaling 1), since they're genes related to oxidative stress and inflammation, two emblems of LD, and they've been preliminarily linked to the molecular pathways in which these microRNAs are involved. Although the commerce between microRNA and their targets frequently leads to the downregulation of the ultimate, there's substantiation of a correlation between high microRNA situations together with an overexpression of their targets. Since Sod2 and Socs1 are response genes for oxidative stress and seditious falls, independently, it's possible that the continued stressed state of 16 mo KO mice could lead to an overexpression of the genes herein anatomized, that parallels the overexpression of miR- 155 as part of the proinflammatory response and the attendant overexpression of miR- 146a, which has been described to ply ananti-inflammatory part in several pathologies that involve impunity responses. Socs1 is a negative controller of cytokine signaling, being convinced by the ultimate, therefore pointing to a part in neutralizing the effect of miR- 155 and the cytokine waterfall convinced with age in LD beast models(as described in). It should be noted that miR- 155 has been proposed as an activator of autophagy, and in hepatic cells infected with hepatitis B contagion, miR- 155 transfection actuated autophagy via the impairment of Socs1/ Akt/ mTOR axis; miR- 155 has also been reported to regulate autophagy and lysosome function in alcoholic liver complaint, as well as the inhibition of mitophagy. Since, in LD, there's substantiation of disabled autophagy and mitophagy, our results showing both an overexpression of miR- 155 and Socs1 could suggest an attempt to promote LB declination in LD mice. These data suggest a implicit remedial part for miR- 155 and miR- 146a for exogenous manipulation, since both microRNAs have been preliminarily related to neuroinflammation in epileptogenic beast models, and they've indeed been proposed as implicit remedial targets for epilepsy. It should be noted, still, that the results herein reported have been entirely attained from manly mice; farther disquisition should be carried out to conclude whether the differences observed in these beast models are generalized or coitus-dependent. To our knowledge, nevertheless, this is the first case in which both microRNAs are described as altered in LD beast models, together with an altered gene expression of apparent gene targets related to oxidative stress, autophagy, and inflammation; therefore, these microRNAs warrant implicit for farther disquisition, which may lead to the description of their specific part as biomarkers for LD progression or indeed as implicit remedial targets.

DISCUSSION

Data analysis was performed with the support of EpiDiseaseS.L. (spin- off from the Center for Biomedical Network Research, CIBER- SCIII, Spain). All reads were aligned using the mouse reference genome (GRCm38 interpretation) from Ensembl. latterly, the number of reads corresponding to mature mouse microRNAs was attained using miRbase v21. The mapping and quantification way were performed using the Subread and Rsubread packages, which comprise a suite of high- performance software programs for recycling coming- generation sequencing data. microRNAs with veritably low counts across all libraries give little substantiation for discriminational expression. These microRNAs were filtered out previous to farther analysis each microRNA demanded to have further than one count per million (CPM) in at least four samples (the size of the lowest group) to be considered, else, the expression of the gene was discarded. latterly, the trimmed mean of M- values(TMM) normalization was performed to exclude composition impulses between libraries. The specific dissipations per microRNA were estimated with the weighted empirical Bayes probability system. The discriminational expression analysis was executed using aquasi-likelihood F- test. Raw p- values were corrected for multiple testing using the Benjamini – Hochberg system and the FDR (false discovery rate) calculated consequently. Before carrying out the discriminational expression analysis, data were explored by generating a multidimensional scaling (MDS) plot. This visualizes the differences between the expression biographies of different samples in two confines. The number of unique and common differentially expressed microRNAs in Epm2a –/ – and Epm2b –/ – samples compared to the control group was represented in Venn plates. In addition, samples were crescively clustered by their gene expression pattern

similarity and represented in a heatmap. powder keg plots were used to represent the proportion of differentially expressed microRNAs attained from the Epm2a –/ –vs. control and Epm2b –/ –vs. control comparisons. The 30 most upregulated microRNAs in both comparisons (FC> 2 and FDR<0.01) were labeled [1-5].

CONCLUSION

Eventually, all RT- qPCR data were captured using the QuantStudio ™ Design and Analysis Software (interpretation1.5.1, Thermo Fisher). The relative expression of each sample was calculated using the 2 – ΔΔCT system (Livak & Schmittgen, 2001), using the CT (cycle threshold) value of RNU6 or sno234 in microRNA analysis, or Gapdh in gene expression analysis, as an internal control for the normalization of the CT of each sample. In the case of microRNA analysis, analogous values were attained for both endogenous controls, with no significant differences in their average CT values. Graphical representations and statistical analyses were conducted using GraphPad Prismv.8.3.0 for Windows

ACKNOWLEDGEMENT

None.

CONFLICT OF INTEREST

None.

REFERENCES

1. **Stanley D, Moore RJ, Wong CH.** An insight into intestinal mucosal microbiota disruption after stroke. *Sci Rep*. 2018;8(1):1-2.
2. **Kuriakose D, Xiao Z.** Pathophysiology and treatment of stroke: Present status and future perspectives. *Int J Mol Sci*. 2020;21(20):7609.
3. **Vidale S, Consoli A, Arnaboldi M, Et al.** Postischemic inflammation in acute stroke. *J Clin Neurol*. 2017;13(1):1-9.
4. **Matsuura M.** Structural modifications of bacterial lipopolysaccharide that facilitate gram-negative bacteria evasion of host innate immunity. *Front Immunol*. 2013;4:109.
5. **Masrori P, Van Damme P.** Amyotrophic lateral sclerosis: A clinical review. *Eur J Neurol*. 2020 Oct;27(10):1918-29.