Tropical Journal of Pharmaceutical Research December 2022; 21 (12): 2625-2631
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v21i12.17

Original Research Article

Genetic changes in fetal cerebral cortex after maternal exposure to sevoflurane

Jing Zhou, Mao Li, Cuicui Shi, Can Qi, Song Ding, Hao Zhang*
Department of Anesthesiology, Huai'an Maternal and Child Health Care Center, The Huai'an Maternity and Child Clinical College of Xuzhou Medical University, Huaian, China

For correspondence:* ***Email:* *hao90513@126.com*

Sent for review: 15 July 2022 *Revised accepted: 30 November 2022*

Abstract

Purpose: *To investigate the acute changes in transcriptome of radial glial progenitor cells after maternal exposure to sevoflurane.*
Methods: *Two groups of sample data were collected from the data set in the GEO database. Pregnant mice in sevoflurane group were exposed to 2.5 % sevoflurane for 6 h on day 14.5 of the pregnancy, while the mice in control group were exposed to 100 % oxygen for 6 h. At the end of the exposure period, the cerebral cortex of the two groups of fetuses was isolated and analyzed by RNA sequencing. Differentially expressed genes (DEG) were analyzed using limma package of R language. The Gene Ontology (GO) and KEGG pathway enrichment were based on DEG through a cluster profile package of R. Moreover, protein-protein interactions (PPI) network construction and central gene prediction were carried out using a string database and R package.*
Results: *Bioinformatics analysis revealed 289 up-regulated genes and 311 down-regulated DEGs, respectively. Gene Ontology and KEGG enrichment analysis revealed terms related to neural development and transcriptional function. Based on the central genes of the PPI network, it was found that certain genes may play significant roles in the regulation of neural development. These genes are hnRNPM, AURKA, NCBP, SRSF6, ASF1B, HNRNPA2B1, DDX21, H3F3B, KPNA2 and ABCE1 ($p < 0.05$).*
Conclusion: *The findings of this study suggest that hub genes and a variety of signal pathways may play key roles in the development of radial glial progenitor cells.*

Keywords: *Bioinformatics, Sevoflurane, Radial glial progenitor*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

In recent times, studies are beginning to pay attention to the effects of general anesthesia on brain development in rodents [1]. When exposed to general anesthesia, the developing nervous system will have obvious neurodegeneration which will eventually lead to the impairment of learning and memory function [1]. Similar conclusions have been obtained in other studies [2,3]. Almost all commonly used narcotic drugs administered in late pregnancy or early life led to impaired neurobehavioral development [2]. In a study on rabbits, it was observed that after pregnant rabbits received sevoflurane general anesthesia, neonatal neurobehavior was

impaired, accompanied by neurodevelopmental restriction [3]. Counting the neurons in several regions of the neonatal rabbit brain, it was found that the number of neurons decreased significantly [3].

So far, the rapid development of microarray technology and high-throughput sequencing technology has resulted in the development of new technology for the diagnosis and treatment of a variety of diseases and has also provided a large number for diagnostic purposes. For example, several studies have begun to use bioinformatics analysis to find potential disease biomarkers, and researchers have searched and analyzed the differential genes of diffused large B-cell lymphoma through bioinformatics and basic experiments, as well as for new possibilities of diagnosis and treatment from possible key pathways [4]. In a study on Alzheimer's disease, the protein-protein interactions (PPI) network was constructed using bioinformatics, and a logistic regression model was constructed for the central genes. These are of value in research for the diagnosis of Alzheimer's disease [5].

Therefore, further research is needed to determine new prognostic molecular biomarkers to help diagnose and find the changes of sevoflurane on the development of radial glial progenitor cells. The purpose of this study was to use bioinformatics methods to identify the changes in the development of radial glial progenitor cells after exposure to sevoflurane, look for the changes in the transcriptome of radial glial progenitor cells after exposure to sevoflurane, and look for the most sensitive and effective biomarkers in these changes. These biomarkers may provide useful clues for the whole change process of cerebral cortex development.

EXPERIMENTAL

Data download and data processing

In order to explore the potential effect of sevoflurane on fetal brain development, the appropriate genome in the NCBI-GEO database, and GSE166607 was downloaded and screened to meet the requirements. The data were divided into two groups: the sevoflurane group (3 samples) and the control group (3 samples). Pre-pregnancy mice in the sevoflurane group were exposed to 2.5 % sevoflurane for 6 h on day 14.5 of the pregnancy, while the control group was exposed to 100 % oxygen for 6 h. At the end of the exposures, the fetal cerebral cortex of the two groups was isolated and analyzed using RNA sequencing. These mRNA maps were based on platform GPL24247 Illumina NovaSeq 6000. This study identified Differentially expressed genes (DEGs) using the limma package in R software (version 3.5.2). The $|Log_2FC| > 0.5$ and P-value < 0.05 were considered as criteria for the identification of DEGs.

Functional enrichment analysis

In order to determine the biological function of DEGs, Gene Ontology (GO) and KEGG pathways were analyzed through the David database. Significant results such as molecular function (MF), biological process (BP), cellular component (CC), and biological pathway were selected with $p < 0.05$.

PPI network of DEGs

This study used the online database Search Tool for the Retrieval of Interacting Genes (STRING) (version 11.0) (https://string-db.org/) to predict and analyze functional connections and potential protein-protein interactions (PPI) among the overlapping genes and reserved the interaction pairs with a confidence score ≥ 0.4. The 30 genes with the most adjacent nodes were chosen for further investigation using R software.

RESULTS

Gene analysis for database

The heat map shows the expression level of all genes (Figure 1). All different genes are shown in the cluster volcano map (Figure 2). The expression of the two groups of genes is very different, which means that these genes contribute to the protection of cardiomyocytes.

GO and KEGG analysis of integrated DEGs

This study used the cluster Profiler R package to perform GO function annotation and KEGG pathway enrichment analysis. The GO function terms were divided into the biological process (BP), molecular function (MF), and cell component (CC) categories. The cutoff value was set as $p < 0.05$.

The top 5 BP terms were enriched among DEGs such as RNA splicing, DNA-templated, mRNA processing, and negative regulation of transcription from RNA polymerase II promoter (Table 1). The top 5 CC terms were nucleus, nucleoplasm, nucleolus, kinetochore, and nuclear chromosome (Table 2).

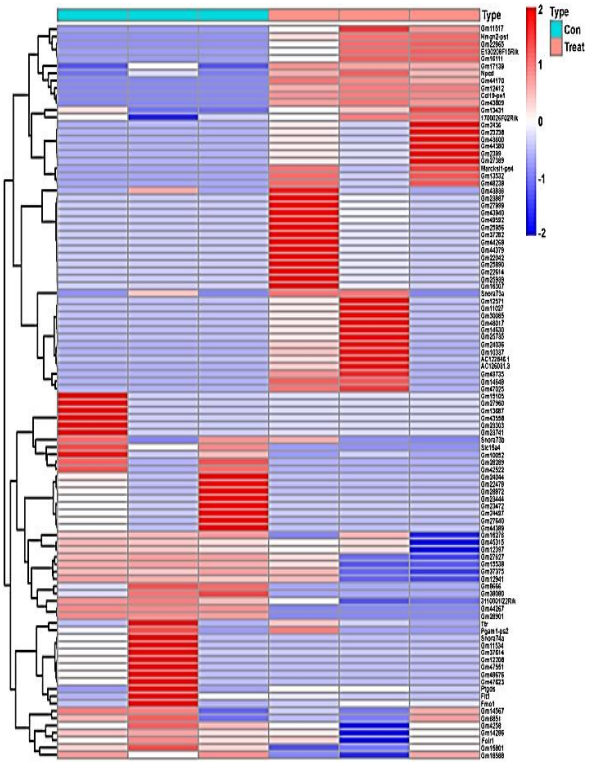

Figure 1: Heat map of all genes. Red indicates up-regulated genes and blue indicates down-regulated genes

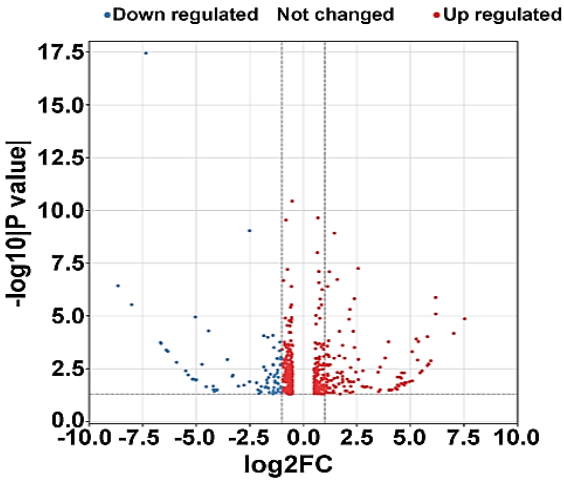

Figure 2: Volcanic map of all genes. Green represents down-regulated genes and black represents unchanged genes. $p <$ 0.05, differential expression | log2FC | > 0.5

The top 5 MF terms were poly(A) RNA binding, RNA binding, nucleic acid binding, nucleotide binding, and metal ion binding (Table 3). Based on KEGG pathway enrichment analysis, the main enrichment pathways were the mRNA surveillance pathway, spliceosome, RNA transport, arginine, and proline metabolism, and biosynthesis of amino acids (Table 4).

PPIs for the DEGs

To further understand the relationship among these genes, this study utilized the string online data (http://string-db.org) to conduct a network analysis of protein-protein interactions for these genes, and then extracted the most interconnected genes as core genes. Results showed that the 30 genes with the highest interaction levels were maintained, including hnRNPM, Aurka, Ncbp, Srsf6, Asf1b, Hnrnpa2b1, Ddx21, H3f3b, Kpna2, and Abce1 (Figure 3).

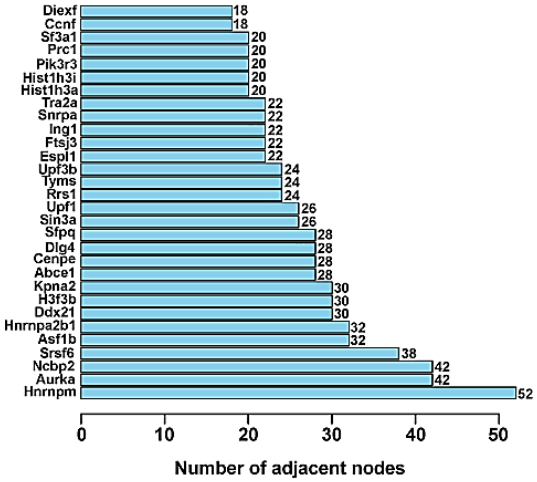

Figure 3: Genes with the highest interaction degrees

DISCUSSION

Since its discovery, sevoflurane has gradually become a popular anesthetic because of its stable, colorless, and non-irritating characteristics [6]. At present, global attention has begun to pay attention to the possible changes in the central nervous system (CNS) after exposure to anesthesia, affecting long-term neural activities. This event has a potential public health impact [7]. Studies on rodents have shown that exposure to general anesthetics in the early postpartum period induced cell death, impaired synaptic growth and neurogenesis, and subsequent cognitive and behavioral problems [8]. Almost all commonly used anesthetics, including sevoflurane, cause neurotoxicity. Neurotoxicity observed in animals lead to neuronal cell death and subsequent learning and memory impairment [8].

Bioinformatics analysis screens candidate genes that may affect neural development through gene differential expression, which provides a strong support for further study of neural development. Through bioinformatics analysis, it was revealed that a series of biological changes and screened the

Table 1: The top 5 biological processes (BP)

Term	Count	%	*P*-value	Genes
GO:0008380~RNA splicing	19	3.92	9.76E-07	ZFP326, PRPF38B, SF3A1, NCBP2, RBM4B, CRNKL1, IWS1, JMJD6, THOC6, RBM4, HNRNPM, SFPQ, HNRNPA2B1, TRA2A, SNRNP48, PRPF31, SRSF6, RBM10, RBM5
GO:0006351~transcription, DNA-template	65	13.40	3.65E-06	PRDM8, ZFP326, ZCCHC12, KDM5C, CHD9, CHD2, CCAR1, SNAPC5, HMGN5, SALL1, SFR1, SIN3A, EPC1, SOX4, RBM14, KDM2A, NCOA5, LMO3, DYNLL1, PPRC1, ZHX1, EMSY, JMJD6, SAP30, SFPQ, SLTM, PSPC1, MED20, TXNIP, ZSCAN26, LRIF1, AJUBA, IRF9, ASF1B, ZFP787, KDM3A, GTF3C6, FLII, FOXG1, CEBPG, AKAP8, DDX21, IWS1, NHLH1, SAFB2, GPBP1L1, BEND6, SPDEF, HEXIM2, CBX6, MYEF2, JUND, NFYA, CBX2, BCL6, TEF, PAGR1A, ID2, BRMS1L, ID1, PPP1R1B, ID3, ZFP592, MPHOSPH8, RCOR1,
GO:0006355~regulation of transcription, DNA-template	73	15.05	1.03E-05	PRDM8, ZFP326, ZCCHC12, KDM5C, CHD9, CHD2, CCAR1, SNAPC5, HMGN5, SALL1, SFR1, SIN3A, GM4724, EPC1, SOX4, ZFP810, RBM14, KDM2A, NCOA5, LMO3, ZFP658, DYNLL1, PPRC1, ZHX1, EMSY, JMJD6, SAP30, MYCL, SFPQ, SLTM, PSPC1, MED20, TXNIP, ZSCAN26, GM4631, LRIF1, ZFP454, AJUBA, IRF9, ASF1B, ZFP787, KDM3A, RGS19, FLII, FOXG1, CEBPG, PRDM15, AKAP8, IWS1, NHLH1, GM14308, SAFB2, GPBP1L1, BEND6, SPDEF, HEXIM2, CBX6, JUND, NFYA, CBX2, 2610008E11RIK, YEATS2, BCL6, TEF, ID2, BRMS1L, ID1, ID3, ZFP592, ZFP790, NUP35, MPHOSPH8, RCOR1
GO:0006397~mRNA processing	20	4.12	1.54E-05	ZFP326, PRPF38B, SF3A1, NCBP2, RBM4B, CRNKL1, IWS1, JMJD6, THOC6, RBM4, HNRNPM, SFPQ, FIP1L1, HNRNPA2B1, TRA2A, FASTKD5, SNRNP48, PRPF31, SRSF6, RBM5
GO:0000122~negative regulation of transcription from RNA polymerase II promoter	29	5.98	3.92E-04	KDM5C, FOXG1, CXXC5, SALL1, SIN3A, EPC1, RBM10, HIST1H1C, SPDEF, HEXIM2, CBX6, MYEF2, JUND, CBX2, DUSP26, ZHX1, VEGFA, SAP30, SFPQ, YEATS2, BCL6, ID2, BRMS1L, HNRNPA2B1, ID1, TXNIP, ID3, AJUBA, RCOR1

Table 2: The top 5 cell components (CC)

Term	Count	%	*P*-value
GO:0005634~nucleus	182	37.52577	2.37E-14
GO:0005654~nucleoplasm	77	15.87629	2.27E-10
GO:0005730~nucleolus	39	8.041237	4.61E-07
GO:0000776~kinetochore	9	1.85567	0.001839
GO:0000228~nuclear chromosome	6	1.237113	0.003

Table 3: The top 5 molecular functions (MF)

Term	Count	%	*P*-value	Genes
GO:0044822 ~poly(A) RNA binding	66	13.61	3.08E-15	ZFP326, POP1, ZFP207, GPATCH4, APEH, CHD2, ELAVL2, CCAR1, DUSP11, RBM4, HMGN5, CSRP1, RAVER1, KPNA2, METTL16, RBM12B2, RBM5, HIST1H1C, RBM12B1, UPF1, RBM14, NCOA5, NCBP2, CIRBP, PPRC1, CRNKL1, DIEXF, REXO4, FTSJ3, SFPQ, 2310033P09RIK, SLTM, PSPC1, FASTKD5, TOP1, HNRNPH3, SRSF6, EIF1A, H2-D1, HEATR1, AKAP8, DDX21, RBM4B, FIP1L1, TRA2A, SAFB2, RRS1, IGF2BP1, H1FX, IGF2BP2, RBM12, RBM10, TRMT1L, SF3A1, PRPF38B, MYEF2, CCDC137, MFAP1A, HIST1H4M, UPF3B, MCAT, HNRNPM, ALDH6A1, H1F0, HNRNPA2B1, PRPF31
GO:0003723 ~RNA binding	39	8.04	3.62E-07	DDX21, RBM4B, ELAVL2, DUSP11, RBM4, FIP1L1, RAVER1, SIN3A, TRA2A, IGF2BP1, SAFB2, DGCR8, IGF2BP2, NUDT16, RBM12B2, RBM12, RBM5, TRMT1L, RBM10, RBM12B1, UPF1, SF3A1, RBM14, NCBP2, CIRBP, PPRC1, CRNKL1, JMJD6, THOC6, HNRNPM, SFPQ, SLTM, PSPC1, HNRNPA2B1, FASTKD5, PRPF31, SRSF6, EIF1A, RPL37RT
GO:0003676 -nucleic acid binding	46	9.48	6.65E-05	PRDM8, ZFP787, ZCCHC12, PINX1, PRDM15, DDX21, RBM4B, GPATCH4, ELAVL2, RBM4, SALL1, RAVER1, ZFP180, GM4724, TRA2A, GM14308, IGF2BP1, SAFB2, IGF2BP2, RBM12B2, RBM12, ZBED4, RBM5, RBM10, RBM12B1, ZFP810, RBM14, MYEF2, NCBP2, ZFP658, CIRBP, 2610008E11RIK, PPRC1, REXO4, HNRNPM, SFPQ, BCL6, SLTM, PSPC1, HNRNPA2B1, ZFP592, ZFP790, ZSCAN26, GM4631, SRSF6, ZFP454
GO:0000166 ~nucleotide binding	61	12.58	3.47E-04	FLT1, CHD9, PYGM, CHD2, NUBP1, ELAVL2, RBM4, HINT2, RAVER1, SPEG, NUDT16, RBM12B2, RBM5, XYLB, RBM12B1, CDKL3, UPF1, ENTPD1, RBM14, RPS6KL1, NCBP2, PRKCD, CIRBP, LMTK3, PPRC1, SFPQ, SLTM, PSPC1, TNIK, HNRNPH3, SRSF6, AGAP2, DDX21, RBM4B, AK4, TYMS, AURKA, MAT2A, STK36, TRA2A, SAFB2, IGF2BP1, IGF2BP2, IP6K1, RBM12, RBM10, REM2, MYEF2, DMPK, UPF3B, UPF3A, CLK1, HNRNPM, CENPE, PFKL, ETNK1, HNRNPA2B1, SPAG1, NUP35, IARS, ABCE1
GO:0046872 ~metal ion binding	90	18.56	0.002029	PRDM8, ZFP326, ZCCHC12, KDM5C, ZFP207, PHF23, RFESD, ITGA2B, CIB2, ECE1, ZC3H6, NENF, HSCB, ZFAND1, SLC6A1, ENO2, ING1, LOXL1, NUBP1, ALKBH3, RBM4, SALL1, CSRP1, CAR15, GM4724, CHORDC1, DGCR8, NUDT16, RNF150, RBM5, ZFP810, UPF1, KDM2A, LMO3, ZFP658, TESC, PRKCD, LMTK3, ZHX1, JMJD6, SAP30, ADAM1A, CDH13, TRIM59, ASPHD2, AMY1, ZSCAN26, GM4631, DNASE1L2, ZFP454, NPTXR, AJUBA, ZFP787, KDM3A, PRDM15, AKAP8, AGAP2, NRXN2, RBM4B, CXXC5, PDF, MAT2A, STK36, CBS, ZFP180, GM14308, PLAGL2, CDH24, PDLIM4, ZSWIM5, ZBED4, RBM10, TRMT1L, SYT5, PRNP, DMPK, KCNIP2, APEX2, 2610008E11RIK, MT2, DNAJA1, RNF146, PFKL, P4HA1, BCL6, ZFP592, ZFP790, SNRNP48, RPL37RT, YPEL3

Table 4: The top5 KEGG pathway

Term	Count	%	*P*-value	Genes
mmu03015:mRNA surveillance pathway	7	1.443299	0.004252	UPF1, FIP1L1, NCBP2, GM2436, UPF3B, UPF3A, SMG7
mmu03040:Spliceosome	8	1.649485	0.005321	HNRNPM, PRPF38B, SF3A1, NCBP2, TRA2A, PRPF31, SRSF6, CRNKL1
mmu03013:RNA transport	9	1.85567	0.005769	UPF1, POP1, NCBP2, NUP50, UPF3B, NUP35, UPF3A, EIF1A, THOC6
mmu00330:Arginine and proline metabolism	5	1.030928	0.007578	P4HA1, ALDH1B1, AMD1, ODC1, SAT2
mmu01230:Biosynthesis of amino acids	5	1.030928	0.033076	PFKL, MAT2A, CBS, ENO2, PRPS1L3

regulatory factors that play a role in these processes, so as to provide candidate genes for further study of specific phenomena.

Heterogeneous nuclear ribonucleoprotein m (hnRNPM) is a gene with the highest correlation in the PPI network. It belongs to one of the molecules of the subfamily of heterogeneous nuclear ribonucleoproteins (hnRNPs) [9]. This family is a kind of protein that exists in the nucleus and can shuttle back and forth between the nucleus and cytoplasm. It often binds to other proteins and proteins have different biological effects [10,11].

In recent years, many studies have focused on the role of hnRNPM in various cancers. Some subfamilies of hnRNPs are abnormally expressed in malignant tissues of various cancers. Interestingly, the expression level of hnRNPs in different cancer tissues is different, for example, in relatively normal tissues, liver cancer tissues, breast cancer tissues and rectal cancer tissues, the expression level of hnRNPs is higher [12-14]. However, the expression level of hnRNPs was decreased significantly in lung cancer and prostate cancer [15,16]. The reason why hnRNPs play different roles in tumors from different tissue sources may be that the target genes of hnRNPs participate in different signal pathways and physiological functions. This shows that the way hnRNPs play a role is very changeable and important.

In a study on the prostate, when the expression of hnRNPM increased, the expression of Twist1 in prostate cancer cells decreased significantly, and it was observed that the migration and invasion of PCa cells *in vitro* were significantly inhibited [16]. In addition, the researchers also found that in the hypoxic tumor microenvironment of rectal cancer, hypoxia increased the binding of hnRNPM in the cytoplasm to its target mRNA and accelerated the initiation of the translation process [17].

HnRNPM often acts as a splicing factor to alter the process of tumor cell invasion and metastasis. It is well known that CD44 cell adhesion molecules are abnormally expressed in many breast tumors, and CD44 splice variants are related to specific carcinogenic signaling pathways. However, patients with high hnRNPM found in breast cancer often have higher levels of CD44 and poorer prognosis [18]. The expression of hnRNPM in a variety of tumors shows that it has the potential as a therapeutic target.

In addition to extensive research on cancer, hnRNPM, as a binding protein, has also been studied for its effects in regulating brain function, and the knockdown of hnRNPM in the CA1 hippocampal region of the mouse brain can lead to learning and memory impairment, the study said. The researchers observed that when hnRNPM was knocked out *in vivo*, it was no longer expressed, and then the morphology of dendritic spines would change, affecting the physiological spine. When hnRNPM binds to synaptophysin and PSD95, the downstream mRNA expression is stable, which regulates the structure and function of neurons [19]. In *Drosophila* species, it was also confirmed that the consumption of hnRNPM was related to the loss of the dendritic terminal branches of neurons [20].

Limitations of this study

This study was mainly based on bioinformatics and lacks further experimental demonstration. It is necessary to further verify it in animal experiments and cell experiments in the future. Additional work is needed to clarify the molecular mechanisms involved in this challenging disease. Further studies are needed to verify the role of hnRNPM in neural development when exposed to sevoflurane at embryonic stage.

CONCLUSION

A comprehensive analysis of the data from the GEO dataset has been conducted and it shows that hnRNPM may be a potential diagnostic biomarker that plays a key role in neurodevelopment. In addition to hnRNPM, a large number of differential genes has been screened. These genes reveal the potential manner in which sevoflurane affects neural development in the embryonic cerebral cortex.

DECLARATIONS

Acknowledgements

None provided.

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the

current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

Open Access

REFERENCES

1. *Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, Olney JW, Wozniak DF. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci 2003; 23(3): 876-882.*
2. *Bleeser T, Van Der Veeken L, Fieuws S, Devroe S, Van de Velde M, Deprest J, Rex S. Effects of general anaesthesia during pregnancy on neurocognitive development of the fetus: a systematic review and meta-analysis. Br J Anaesth 2021; 126(6): 1128-1140.*
3. *Devroe S, Van der Veeken L, Bleeser T, Van der Merwe J, Meeusen R, Van de Velde M, Deprest J, Rex S. The effect of xenon on fetal neurodevelopment following maternal sevoflurane anesthesia and laparotomy in rabbits. Neurotoxicol Teratol 2021; 87: 106994.*
4. *Li Q, Meng Y, Hu L, Charwudzi A, Zhu W, Zhai Z. Integrative analysis of hub genes and key pathway in two subtypes of diffuse large B-cell lymphoma by bioinformatics and basic experiments. J Clin Lab Anal 2021; 35(11): e23978.*
5. *Wang H, Zhang Y, Zheng C, Yang S, Chen X, Wang H, Gao S. A 3-gene-based diagnostic signature in Alzheimer's disease. Eur Neurol 2022; 85(1): 6-13.*
6. *Wang H, Wang B, Jing J, Li N. Sevoflurane induces lung cancer cell apoptosis via inhibition of the expression of miRNA155 gene. Trop J Pharm Res 2021; 20(1):69-74 doi: 10.4314/tjpr.v20i1.11*
7. *Vutskits L, Davis PJ, Hansen TG. Anesthetics and the developing brain: time for a change in practice? A pro/con debate. Paediatr Anaesth 2012; 22(10): 973-980.*
8. *Lin EP, Soriano SG, Loepke AW. Anesthetic neurotoxicity. Anesthesiol Clin 2014; 32(1): 133-155.*
9. *Pinol-Roma S, Dreyfuss G. hnRNP proteins: localization and transport between the nucleus and the cytoplasm. Trends Cell Biol 1993; 3(5): 151-155.*
10. *Pinol-Roma S. HnRNP proteins and the nuclear export of mRNA. Semin Cell Dev Biol 1997; 8(1): 57-63.*
11. *Cho S, Moon H, Loh TJ, Oh HK, Cho S, Choy HE, Song WK, Chun JS, Zheng X, Shen H. hnRNP M facilitates exon 7 inclusion of SMN2 pre-mRNA in spinal muscular atrophy by targeting an enhancer on exon 7. Biochim Biophys Acta 2014; 1839(4): 306-315.*
12. *Honore B, Baandrup U, Vorum H. Heterogeneous nuclear ribonucleoproteins F and H/H' show differential expression in normal and selected cancer tissues. Exp Cell Res 2004; 294(1): 199-209.*
13. *Ushigome M, Ubagai T, Fukuda H, Tsuchiya N, Sugimura T, Takatsuka J, Nakagama H. Up-regulation of hnRNP A1 gene in sporadic human colorectal cancers. Int J Oncol 2005; 26(3): 635-640.*
14. *Xu Y, Gao XD, Lee JH, Huang H, Tan H, Ahn J, Reinke LM, Peter ME, Feng Y, Gius D, et al. Cell type-restricted activity of hnRNPM promotes breast cancer metastasis via regulating alternative splicing. Genes Dev 2014; 28(11): 1191-1203.*
15. *Pio R, Zudaire I, Pino I, Castano Z, Zabalegui N, Vicent S, Garcia-Amigot F, Odero MD, Lozano MD, Garcia-Foncillas J, et al. Alpha CP-4, encoded by a putative tumor suppressor gene at 3p21, but not its alternative splice variant alpha CP-4a, is under-expressed in lung cancer. Cancer Res 2004; 64(12): 4171-4179.*
16. *Yang T, An Z, Zhang C, Wang Z, Wang X, Liu Y, Du E, Liu R, Zhang Z, Xu Y. hnRNPM, a potential mediator of YY1 in promoting the epithelial-mesenchymal transition of prostate cancer cells. Prostate 2019; 79(11): 1199-1210.*
17. *Chen TM, Lai MC, Li YH, Chan YL, Wu CH, Wang YM, Chien CW, Huang SY, Sun HS, Tsai SJ. hnRNPM induces translation switch under hypoxia to promote colon cancer development. Ebiomedicine 2019; 41: 299-309.*
18. *Sun H, Liu T, Zhu D, Dong X, Liu F, Liang X, Chen C, Shao B, Wang M, Wang Y. HnRNPM and CD44s expression affects tumor aggressiveness and predicts poor prognosis in breast cancer with axillary lymph node metastases. Genes Chromosomes Cancer 2017; 56(8): 598-607.*
19. *Akinyemi AR, Li D, Zhang J, Liu Q. hnRNPM deficiency leads to cognitive deficits via disrupting synaptic plasticity. Neurosci Lett 2021; 751: 135824.*
20. *Xu X, Brechbiel JL, Gavis ER. Dynein-dependent transport of nanos RNA in drosophila sensory neurons requires rumpelstiltskin and the germ plasm organizer Oskar. J Neurosci 2013; 33(37): 14791-14800.*