RESEARCH PAPER

Influence of Female Reproductive Hormone on MiRNA expression

Suganya. S[1], Dr Senthil Kumar[2], Dr Shankar[3], Dr. Lakshmipathy Ramesh[4], N. Stanley Vinoth[5], Dr Ben Sundra Ashok[6]

[1]Department of physiology Research scholar, Sri Ramachandra Institute of Higher Education and Research
[2]Registrar Sri Ramachandra institute of higher education and Research
[3]MD Department of neurology Sundaram foundation
[4]Founder & Director of Geri Care;
[5]Department of Psychiatry, Sri Ramachandra Institute of Higher Education and Research (SRIHER), Porur, Chennai;
[6]Head, Clinical Laboratory, NURA- Fujifilm
Corresponding Author
Suganya S
Department of physiology Research scholar, Sri Ramachandra Institute of Higher Education and Research
EMAIL- ssysrmc@gmail.com

ABSTRACT
Advancements in medicine have increased life expectancy, notably impacting women's health due to lower estrogen levels post-menopause, which can contribute to age-related disorders like Alzheimer's and mood disorders. 17β-estradiol (E2), a key hormone, affects neuroprotection and cognitive functioning by influencing neurotransmission and gene expression through estrogen receptors (ER). MicroRNAs (miRNAs) also play crucial roles in regulating physiological processes and are implicated in neurological functions and disorders, particularly in women as they age. Dysregulation of miRNAs can lead to conditions affecting the brain, heart, and lungs. The interaction between E2 and miRNAs in the brain suggests that estrogen modulates miRNA expression, affecting cognitive health. Estrogen receptors regulate miRNA biogenesis, affecting gene transcription and potentially serving as biomarkers for estrogen-related diseases. Further research is necessary to clarify estrogen's relationship with miRNA expression and its implications for neuroprotection.
Keywords: Estrogen, cognitive function, neuroprotection
How to cite this article Suganya. S, Dr Senthil Kumar, Dr Shankar, Dr. Lakshmipathy Ramesh, N. Stanley Vinoth, Dr Ben Sundra Ashok Influence of Female Reproductive Hormone on MiRNA expression Int J Drug Deliv Technol. 2026;16(90s): 151-157; DOI: 10.25258/ijddt.16.90s.15
Source of support: Nil. ,
Conflict of interest: None

1.INTRODUCTION

Advancement in medicine and change in life style have increased the human life expectancy (Arias E, 2014). Particularly women survive longer than men. This alteration in life span makes the women to live with low estrogen constantly over a period of time which might lead to age related disorders like Alzheimer's, dementia, and mood disorders. 17β-estradiol (E2) is the major circulating female reproductive hormone that is required for many physiological functions especially in brain. E2 is a steroid hormone plays a major role in neuroprotection .It reduces the risk of cognitive decline and enhance the neurotransmission via neurotransmitters. When the women attains post-menopausal period, the level of E2 falls below 50 pg/ml that leads to loss of protective function andcognitive dysfunction. Estrogen effects are interposed by the estrogen receptor (ER) that confine to DNA and regulates gene expression. It controls the transcription of DNA base and translocation of the base excision repair enzymes among distinct intracellular compartments. Micro RNA's (miRNA's) is a short regulatory non-coding RNA's which directly modulate estrogen-dependent gene expression through decreasing ERα mRNA stability or translation. It regulates various biological functions by the translation of genes encoding proteins. Recent investigations have showed that miRNAs are implicated in the control of brain development and functions. Reproductive hormones especially estrogen has an ability to regulate microRNA expression (Lam EW, 2012). It binds which influences gene expression, either directly or indirectly, to nuclear hormone receptors there is progressive decline in estrogen as age increases, which would results in alteration of MiRNA expression. The dysregulation of microRNAs leads to various pathologic conditions of the heart, lung and brain (Abe M, 2013). Expressions of MiRNAs differs in males and females (Marco A, 2013) . However, there is no much literature available to justify whether estrogen regulate any proteins that are linked to miRNAs stabilization pathways but still it exists as a hypothesis. Hence in this review we emphasize the role of female reproductive hormone on biosynthesis of MiRNAs. Identification of estrogen regulated MiRNA can be used as a biomarker in estrogen associated diseases.

MiRNAs in CNS:

MicroRNAs regulate various physiological processes like cell growth, development, morphogenesis, maturation and apoptosis (Zhou Y, 2013). Micro RNA's takes part in various neurological functions including neuronal

*Author for Correspondence: - ssysrmc@gmail.com

development (miR-430, miR-9, miR-10) (Delaloy C, 2010) and neuronal cell maintenance (miR-29a/b, miR-134) (Lippi G,2011). The expression of MiRNAs is found to be down regulated as age advances which leads to neurodegenerative disorders (Kumar A, 2013). MiR-125a/b, miR-495 and miR-181 are dissimulated in Alzheimer's disease. These microRNAs targets the β-site amyloid precursor protein cleaving enzyme-1 (Somel M, 2010). Hormonal regulation of microRNAs is attributed to neurodegenerative disorders (Morgan CP, 2011). It is also speculated that sex chromosomes could regulate microRNAs in neurodegenerative disorders (Morgan CP, 2012).Specific MiRNAs are expressed in brain which involves in maturation of cortical neurons. There is progressive loss of MiRNA, death of Purkinje neurons, and cerebellar degeneration due to deficiency of Dicer, the key ribonuclease in MiRNA biogenesis (Davis TH, 2008). Some miRNAs are involved in regulation of Aβ production which is involved in pathogenesis of AD (Idda ML, 2018). MiR-132 plays a major role in cleavage of Tau protein. Tau is degraded by several proteases facilitating its breakdown and clearance. Accumulation of these fragments become aggregated to form neurotoxic (Rissman RA, 2004). Tau cleavage by calpain 2 produces a 17 kDa neurotoxic fragment that are found in the brains of patients with tauopathy (Reinbeck JB, 2011). Calpain and p35 cleaves Tau, which is the main activator of Cdk5. p35 is converted into p25 that causes hyperactivation of both Cdk5 and GSK3β and consequently tau hyperphosphorylation (Kurbatskaya K, 2016). Thus, miR-132 is a key modulator of Calpain 2 which is found in the nervous tissue that might increase the risk of developing AD. Similarly, miR-101 (Vilardo et al., 2010), miR-16 (Liu et al., 2010) and miR-153 (Long et al., 2012) have also been shown to down-regulate APP expression. In addition, the decreased level of miR-153 was responsible for the formation of Aβ in AD patients. Tiribuzi et al.. (2014) reported that the elevated miR-128 might hinder the clearance of Aβ and the Aβ degradation was improved when it was suppressed. It has been shown that expression levels of miR-125b are dramatically enhanced in non-familial AD patients (Jin et al, 2018). miR-138 expression level is up-regulated in AD patients. Wang et al., (2015) reported that miR-138 might directly target retinoic acid receptor alpha to suppress glycogen synthase kinase-3b (GSK-3β) activity. They also proved that miR-138 was able to induce Tau phosphorylation in N2a/APP and HEK293/tau cells through the RARA/GSK-3β pathway (Wang et al., 2015). There is a remarkable elevation of miR-26b in the brain tissue of AD patients. Some of the MiRNAs such as miR-9 and miR-132 were down regulated in hippocampal area and medial frontal gyrus specific. MiR-124 and miR-128 are neuron-specific whereas miR-23, miR-26 and miR-29 are expressed in astrocytes (Zeng Y, 2009). MiR-195 is differentially expressed in relation to age and shows inversely proportion to age (Von, 2005).The hippocampus region in the brain is responsible for learning and memory which regulates synaptic plasticity. Two miRNAs: miR132 and miR-134 are highly expressed in the hippocampus (Olsen L, 2009). MiR-132 was found to be regulated by BDNF via CREB activation (Magill ST, 2010). Particularly miR-124, miR-125a, miR-9, miR181a and miR-29 gets altered in aging brain (Somel M, 2010).

Regulation of MiRNAs by sex chromosome:

The sex chromosome differentially controls the expression of microRNAs. Males and females differ in their gene expression. Since males have single X chromosome on the gene, they are more likely to suffer from diseases caused by recessive mutations. The X chromosome contains a high density of microRNAs. The X chromosome encodes 113 microRNAs and the Y chromosome only 2, according to microRNA archive (www.miRBase.org 2013). In humans, about 15% of genes encoded by the inactive X chromosome (Song R, 2009), which in some cases results in higher expression of the X gene in females than in males.

MiRNAs and Estrogen:

Estradiol is a well-established key for neurobiological processes, including memory and mood. The risk of developing mild cognitive impairment, dementia and Alzheimer's disease (AD) that affect learning and memory processes is increased in post-menopausal women (Zandi PP, 2002). Estradiol mainly mediates gene transcription through the estrogen receptor α (ERα) and β (ERβ) which bind to the promoter region and induce transcription (Paris O, 2012). Estrogen signalling is closely linked to epigenetic mechanisms. Gene expression is affected by ERs through covalent modifications of histone, microRNAs (miRNAs) and DNA methylation. Some of the co-regulators are involved in the epigenetic mechanism that causes posttranslational changes to the histone proteins. Specific epigenetic changes are required for the of transcription. Moreover, estrogen signalling is potentially influenced by various factors such as different pathologies, aging and environmental factors that may induce epigenetic changes (Kuhlmann JD, 2012). Estrogen receptors in the brain have specific expression patterns, which causes the marked expression of estradiol-responsive genes in the brain in post-menopausal women. E2 plays a major role in miRNA expression the brain. Thus, 5 specific miRNAs have been found to be associated with E2 namely Let-7i, miR-7a, miR-9, miR-9-3p and miR 495.Aging modifies brain miR-7a in regions involved in anxiety and memory (Gao J, 2010). ER alpha affects drosha and participates in the maturation of several miRNAs (Zhang QG, 2009). MiR-9 and miR-9-3p arise from the same primary MiRNA transcript (pri-miRNA) under the control of E2 (Moore RL, 2012).

Estrogen acts through gene transcription by attaching to ER's which serve as transcription factors on gene promoters, in addition to estrogen modulators the gene expression at the post-transcriptional level by microRNAs (miRNA). MiRNAs are small non-coding RNAs that regulate gene expression by translational repression of target mRNAs (Selbach M, 2008) and thus decrease the protein products of those genes. E2 interacts with MiRNA biogenesis by estrogen through several potential regulatory points. Initially RNA polymerase II (Pol II) transcribes miRNAs from the genome. Secondly, the miRNAs are under post-transcriptional control by a series of RNase III enzymes that sequentially cleave the primary transcript (pri-

miRNA) into shorter fragments and work in tandem with several cofactor proteins, some of which are regulated by estrogen (Heo I,2008). E2 regulates miR-26a located in dendrites of neurons. These findings shows that E2 may enhance synaptic plasticity through miR-26a. In the hypothalamus, let-7i, miR-7a, miR-9 and miR-9-3p were regulated by ERβ.MiR-30b was shown to be regulated by estrogen (Mellios N, 2012). It is found that miR-218 is associated with estrogen receptor on Tau phosphorylation. The miR-218 was up-regulated by estrogen receptor α and inhibits protein tyrosine phosphatase α (PTPα) (Xiong, Y.S., 2015). Estrogen has been demonstrated to protect neurons from inflammation by inhibiting the activation of inflammatory markers (Wen, et al., 2004). Thus, the list of ER-regulated miRNAs was tabulated below. However, this protection may be reduced in case of postmenopausal women, making them more susceptible to age related disorders

Table 1: MiRNAs expressed by ERα

Upregulation	**miR-19a,miR-19b,miR-20a,miR 20b,miR-25,miR-101,miR-135a,miR-190a, miR-191 miR-196a2,miR-203,miR-424,miR-425, miR-760, miR-942, miR-944**	CastellanoL,2009;ZhaoJ,2013;Chu HW,2014;DiLevaG,2013;Cicatiello L,2010;FerraroL,2012;KimK,2013; Nagpal N,2013
Down regulation	**let-7g,miR-16,miR-21,miR-23a,miR-26a,miR-26b,miR-27a miR-34b miR-107,miR-125a,miR-140,miR-143, miR-145,miR-181b,miR-181c,miR-195,miR-203,miR-206,miR-221, miR-222, miR-515-5p, miR-570, miR-618**	AdamsBD,2007;CastellanoL,2009; WickramasingheNS,2009;ZhangY,2012; CicatielloL,2010;FerraroL,2012;Pinho FG,2013;LeeYM,2011;YuX,2012; Yamagata K,2009; Di Leva G,2010; Qian P,2011

Table 2: MiRNAs expressed by ERβ:

Upregulation	**miR-10a miR-10b miR-23b miR-24-1 miR-27b miR-191 miR-205**	Paris O,2012; Edvardsson K,2013; Nagpal N,2013
Down regulation	**miR-9 miR-9-3 miR-17 miR-18a miR-18b miR-19a miR-19b miR-20a miR-20b miR-21 miR-24 miR-25 miR-27b miR-30a miR-30b miR-31 miR-92a miR-106a miR-135a miR-135b miR-140-5p miR-142-3p miR-155 miR-183 miR-192 miR-194 miR-196a miR-200a miR-200b miR-221 miR-301a miR-590-5p**	ParisO,2012;Edvardsson K,2013;HeYQ,2012;Queiros AM,2013

Table 3: MiRNA expressed by ERα and/or ERβ-mediated:

Upregulation	**let-7a let-7b let-7c let-7d miR-98 miR-106a miR-128a miR-130blet-7e let-7f let-7g let-7i miR-7 miR-17 miR-18a miR-21 miR-27a miR-92a-1 miR-148a miR-155 miR-182 miR-200b miR-205 miR-223 miR-320 miR-451 miR-486 miR-708**	Zhao J,2013; Nothnick WB,2010; Dai R,2008; Bhat-Nakshatri P,2009; Masuda M,2012; Zhang C,2013; Wang G,2010; ZhangR,2012;Cochrane DR,2010
Down regulation	**let-7e miR-23b miR-27b miR-30c miR-125b miR-126 miR-146a miR-181a miR-200c miR-204 miR-208 miR-429**	Zhao J,2013; Maillot G,2009;NothnickWB,2010; Dai R,2008; Kong X,2014

Table 4: MiRNA expressed by GPER1-:

Down regulation	**miR-338-3p**	Jacovetti C,2012

ER – estrogen receptor; miRNA – microRNA; GPER1 – G protein-coupled estrogen receptor 1 (Vrtacnik P. et al., 2014)

MiRNAs and Progesterone:

Progesterone is a C21-steroid hormone that plays a role in many different physiological function in the body because it is expressed in neurons and glial cells (Baulieu and Robel, 1990). It is regulated via genomic mechanisms of PR (Progesterone Receptor). These PRs belongs to class of nuclear receptors that regulate proliferation, growth and differentiation (Vázquez-Martínez et al., 2014). Human nuclear PR is a single gene which is located on chromosome 11. The expression of major mRNA transcripts encoding through classical PR-A and PR-B that are regulated by two promoters of the PR gene (Patel et al., 2015). Estrogen also activates PR-A/B promoters by binding to the proximal part of the promoters containing estrogen-response-elements (Jacobsen and Horwitz, 2012). Progesterone is involved in regulating neuronal plasticity in normal brain function, and it reduces anxiety and depression (Pineles et al., 2018). Progesterone has an important role in promoting myelination by oligodendrocytes and Schwann cells (Melfi et al., 2017). Progesterone binds to progesterone receptor in the cytoplasm, resulting in receptor dimerization, translocation into the nucleus and trigger regulation of DNA transcription (genomic mechanism) which facilitates synaptogenesis. Several potential miRNA binding sites in the 3' UTR of PR mRNA that may alter expression of these receptors (Toms et al., 2015).Progesterone mediates its effects on CNS via regulation of some miRNAs. Therefore, more knowledge is required to identify the MiRNA regulated by progesterone.

CONCLUSION:

Estrogen signaling and epigenetic regulation are essential to maintain cell and tissue homeostasis. Some of the epigenetic changes are inherent to the transcriptional regulation of estrogen through co-regulators that may enhance the signalling pathway. In this review, we focused on the role of estrogen in miRNA expression. The physiological function of estrogen depends on ER's within intracellular. Furthermore, both age and estrogen can modulate the MiRNA profiles by regulating the MiRNA biosynthesis pathways. Future research is essential to investigate the purpose of Estrogen in the biogenesis of MiRNA expression which plays a vital role in neuroprotection and also serve as a biomarker clinically

REFERENCE

1. Arias E United States life tables, 2010. National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System;2014. 63: 1-63.
2. Abe M, Bonini NM: MicroRNAs and neurodegeneration: role and impact.Trends Cell Biol 2013, 23:30–36.
3. Lam EW, Shah K, Brosens JJ: The diversity of sex steroid action: the role of micro-RNAs and FOXO transcription factors in cycling endometrium and cancer. J Endocrinol 2012, 212:13–25.
4. Marco A, Kozomara A, Hui JH, Emery AM, Rollinson D, Griffiths-Jones S, Ronshaugen M: Sex-biased expression of microRNAs in Schistosoma mansoni. PLoS Negl Trop Dis 2013, 7:2402.
5. Song R, Ro S, Michaels JD, Park C, McCarrey JR, Yan W: Many X-linked microRNAs escape meiotic sex chromosome inactivation. Nat Genet 2009, 41:488–493.
6. Mellios N, Galdzicka M, Ginns E, Baker SP, Rogaev E, Xu J, Akbarian S: Gender-specific reduction of estrogen-sensitive small RNA, miR-30b, in subjects with schizophrenia. Schizophr Bull 2012, 38:433–443.
7. Zhou Y, Jiang H, Gu J, Tang Y, Shen N, Jin Y: MicroRNA-195 targets ADP-ribosylation factor-like protein 2 to induce apoptosis in human embryonic stem cell-derived neural progenitor cells. Cell Death Dis. 2013, 4:695
8. Delaloy C, Liu L, Lee JA, Su H, Shen F, Yang GY, Young WL, Ivey KN, Gao FB: MicroRNA-9 coordinates proliferation and migration of human embryonic stem cell-derived neural progenitors. Cell Stem Cell .2010, 6:323–335
9. Lippi G, Steinert JR, Marczylo EL, D'Oro S, Fiore R, Forsythe ID, Schratt G, Zoli M, Nicotera P, Young KW: Targeting of the Arpc3 actin nucleation factor by miR-29a/b regulates dendritic spine morphology Cell Biol .2011 ; 194:889–904
10. Kumar A, Gibbs JR, Beilina A, Dillman A, Kumaran R, Trabzuni D, Ryten M, Walker R, Smith C, Traynor BJ, Hardy J, Singleton AB, Cookson MR: Ageassociated changes in gene expression in human brain and isolated neurons. Neurobiol Aging 2013, 34:1199–1209.
11. Somel M, Guo S, Fu N, Yan Z, Hu HY, Xu Y, Yuan Y, Ning Z, Hu Y, Menzel C, Hu H, Lachmann M, Zeng R, Chen W, Khaitovich P: MicroRNA, mRNA, and protein expression link development and aging in human and macaque brain. Genome Res 2010, 20:1207–1218.
12. Morgan CP, Bale TL: Early prenatal stress epigenetically programs dysmasculinization in second-generation offspring via the paternal lineage. J Neurosci 2011, 31:11748–11755.
13. Morgan CP, Bale TL: Sex differences in microRNA regulation of gene expression: no smoke, just miRs. Biol Sex Differ 2012, 3:22.
14. Davis TH, Cuellar TL, Koch SM, Barker AJ, Harfe

BD, McManus MT, Ullian EM Conditional loss of Dicer disrupts cellular and tissue morphogenesis in the cortex and hippocampus. Journal of Neuroscience. 2008, 28:4322–4330. https://doi.org/10.1523/ JNEUROSCI.4815-07.2008.

15. Idda ML, Munk R, Abdelmohsen K, Gorospe M .Noncoding RNAs in Alzheimer's disease. Wiley Interdiscip Rev RNA,2018.
16. Rissman RA, Poon WW, Blurton-Jones M, Oddo S, Torp R, Vitek MP et al .Caspase-cleavage of tau is an early event in Alzheimer disease tangle pathology. J Clin Investig.2004, 114:121–130.
17. Reinecke JB, DeVos SL, McGrath JP, Shepard AM, Goncharof DK, Tait DN et al . Implicating calpain in tau-mediated toxicity in vivo.PLoS One 2011, 6:23865. https://doi.org/10.1371/journ al.pone.0023865.
18. Kurbatskaya K, Phillips EC, Croft CL, Dentoni G, Hughes MM, Wade MA et al. Upregulation of calpain activity precedes tau phosphorylation and loss of synaptic proteins in Alzheimer's disease brain. Acta Neuropathol Commun.2016, 4:34.
19. Vilardo, E., Barbato, C., Ciotti, M., Cogoni, C., and Ruberti, F. MicroRNA101 regulates amyloid precursor protein expression in hippocampal neurons. J. Biol. Chem.2010; 285, 18344–18351.
20. Liu, W., Liu, C., Zhu, J., Shu, P., Yin, B., Gong, Y., et al. MicroRNA16 targets amyloid precursor protein to potentially modulate Alzheimer's associated pathogenesis in SAMP8mice.NeurobioliogyAging.2010;33:522–534.
21. Tiribuzi, R., Crispoltoni, L., Porcellati, S., Di Lullo, M., Florenzano, F., Pirro, M., et al. miR128 up-regulation correlates with impaired amyloid β (1-42) degradation in monocytes from patients with sporadic Alzheimer's disease. Neurobiol. Aging.2014; 35: 345–356.
22. Jin, Y., Tu, Q., and Liu, M. MicroRNA-125b regulates Alzheimer's disease through SphK1 regulation. Mol. Med. Rep. 2018;18: 2373–2380.
23. Wang, X., Tan, L., Lu, Y., Peng, J., Zhu, Y., Zhang, Y., et al. MicroRNA-138 promotes tau phosphorylation by targeting retinoic acid receptor alpha. FEBS Lett. 2015; 589: 726–729.
24. Xiong, Y.S.; Liu, F.F.; Liu, D.; Huang, H.Z.; Wei, N.; Tan, L.; Chen, J.G.; Man, H.Y.; Gong, C.X.; Lu, Y.; et al. Opposite effects of two estrogen receptors on tau phosphorylation through disparate effects on the miR-218/PTPA pathway. Aging Cell 2015, 14, 867–877.
25. Zeng Y. Regulation of the mammalian nervous system by microRNAs. Mol Pharmacol. 2009; 75:259–264.
26. Vo N, Klein ME, Varlamova O, Keller DM, Yamamoto T, Goodman RH, Impey S. A cAMP response element binding protein-induced microRNA regulates neuronal morphogenesis. Proc Natl Acad Sci U S A. 2005; 102:16426–164.
27. Olsen L, Klausen M, Helboe L, Nielsen FC, Werge T . MicroRNAs show mutually exclusive expression patterns in the brain of adult male rats.2009; PLoS One 4: 7225
28. Magill ST, Cambronne XA, Luikart BW, Lioy DT, Leighton BH, et al. microRNA132 regulates dendritic growth and arborization of newborn neurons in the adult hippocampus. Proc Natl Acad Sci U S A.2010; 107: 20382-20387.
29. Somel M, Guo S, Fu N, Yan Z, Hu HY, et al. MicroRNA, mRNA, and protein expression link development and aging in human and macaque brain. Genome Res.2010; 20: 1207- 1218.
30. Zandi PP, Carlson MC, Plassman BL, Welsh-Bohmer KA, Mayer LS, et al. Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. Jama.2002; 288: 2123-2129.
31. Paris O, Ferraro L, Grober OM, Ravo M, De Filippo MR, et al. Direct regulation of microRNA biogenesis and expression by estrogen receptor beta in hormone-responsive breast cancer. Oncogene.2012; 31: 4196-4206.
32. Gao J, Wang WY, Mao YW, Graff J, Guan JS, et al. A novel pathway regulates memory and plasticity via SIRT1 and miR-134. Nature .2010; 466: 1105-1109.
33. Zhang QG, Raz L, Wang R, Han D, De Sevilla L, et al. Estrogen attenuates ischemic oxidative damage via an estrogen receptor alpha-mediated inhibition of NADPH oxidase activation. J Neurosci .2009; 29: 13823-13836.
34. Moore RL, Dai Y, Faller DV . Sirtuin 1 (SIRT1) and steroid hormone receptor activity in cancer. J Endocrinol .2012; 213: 37-48.
35. Selbach M, Schwanhausser B, Thierfelder N, Fang Z, Khanin R, et al. Widespread changes in protein synthesis induced by microRNAs. Nature .2008;455: 58-63
36. De N, Young L, Lau PW, Meisner NC, Morrissey DV, et al. Highly complementary target RNAs promote release of guide RNAs from human Argonaute2. Mol Cell.2013; 50: 344-355.
37. Baulieu EE, Robel P. Neurosteroids: a new brain function? J Steroid Biochem Mol Biol.1990; 37(3):395–403.
38. Vázquez-Martínez ER, Mendoza-Garcés L, Vergara-Castañeda E, Cerbón M. Epigenetic regulation of progesterone receptor isoforms: from classical models to the sexual brain. Mol Cell Endocrinol.2014 392(1-2):115–124.
39. Patel B, Elguero S, Thakore S, Dahoud W, Bedaiwy M, Mesiano S. Role of nuclear progesterone receptor isoforms in uterine pathophysiology. Hum Reprod Update.2015; 21(2):155–173.
40. Jacobsen BM, Horwitz KB. Progesterone receptors, their isoforms and progesterone regulated transcription. Mol Cell Endocrinol.2012; 357: 18–29
41. Pineles SL, Nillni YI, Pinna G, Irvine J, Webb A,

Arditte Hall KA, Hauger R, Miller MW, Resick PA, Orr SP, et al. PTSD in women is associated with a block in conversion of progesterone to the GABAergic neurosteroids allopregnanolone and pregnanolone measured in plasma. Psychoneuroendocrinology.2018; 93:133–141.
42. Melfi S, Montt Guevara MM, Bonalume V, Ruscica M, Colciago A, Simoncini T, Magnaghi V. Src and phospho-FAK kinases are activated by allopregnanolone promoting Schwann cell motility, morphology and myelination.2017.
43. Toms D, Xu S, Pan B, Wu D, Li J. Progesterone receptor expression in granulosa cells is suppressed by microRNA-378-3p. Mol Cell Endocrinol.2015; 399:95–102.
44. Wen Y, Yang S, Liu R, Perez E, Yi KD, Koulen P, Simpkins JW. Estrogen attenuates nuclear factor-kappa B activation induced by transient cerebral ischemia. Brain Res. 2004; 1008:147–154.
45. Kuhlmann JD, Rasch J, Wimberger P, Kasimir-Bauer S. microRNA and the pathogenesis of ovarian cancer - a new horizon for molecular diagnostics and treatment? Clin Chem Lab Med 2012; 50:601-15.
46. Castellano L, Giamas G, Jacob J, Coombes RC, Lucchesi W,Thiruchelvam P, et al. The estrogen receptor-alpha-induced microRNA signature regulates itself and its transcriptionalresponse.Proc.Natl.Acad.Sci.USA20 09; 106:15732.
47. Zhao J, Imbrie GA, Baur WE, Iyer LK, Aronovitz MJ, Kershaw TB, et al. Estrogen receptor-mediated regulation of microRNA inhibits proliferation of vascular smooth muscle cells. Arterioscler Thromb Vasc Biol 2013; 33:257-65.
48. Chu HW, Cheng CW, Chou WC, Hu LY, Wang HW, Hsiung CN, et al. A novel estrogen receptor-microRNA 190a-PAR-1-pathway regulates breast cancer progression, a finding initially suggested by genome-wide analysis of loci associated with lymph-node metastasis. Hum Mol Genet 2014; 23:355- 67.
49. Di Leva G, Piovan C, Gasparini P, Ngankeu A, Taccioli C, Briskin D, et al. Estrogen mediated-activation of miR191/425 cluster modulates tumorigenicity of breast cancer cells depending on estrogen receptor status. PLoS Genet 2013; 9:e1003311.
50. Cicatiello L, Mutarelli M, Grober OM, Paris O, Ferraro L, Ravo M, et al. Estrogen receptor alpha controls a gene network in luminal-like breast cancer cells comprising multiple transcription factors and microRNAs. Am J Pathol 2010; 176:2113-30.
51. Ferraro L, Ravo M, Nassa G, Tarallo R, De Filippo MR, Giurato G, et al. Effects of oestrogen on microRNA expression in hormone-responsive breast cancer cells. Horm Cancer 2012;3:65-78.
52. Kim K, Madak-Erdogan Z, Ventrella R, Katzenellenbogen BS. A MicroRNA196a2* and TP63 circuit regulated by estrogen receptor-alpha and ERK2 that controls breast cancer proliferation and invasiveness properties. Horm Cancer 2013; 4:78- 91.
53. Nagpal N, Ahmad HM, Molparia B, Kulshreshtha R. MicroRNA-191, an estrogen-responsive microRNA, functions as an oncogenic regulator in human breast cancer. Carcinogenesis 2013; 34:1889-99. http://dx.doi.org/10.1093/carcin/bgt107.
54. Adams BD, Furneaux H, White BA. The micro-ribonucleic acid (miRNA) miR-206 targets the human estrogen receptor-alpha (ER alpha) and represses ER alpha messenger RNA and protein expression in breast cancer cell lines. Mol. Endocrinol. 2007; 21:1132-47.
55. Wickramasinghe NS, Manavalan TT, Dougherty SM, Riggs KA, Li Y, Klinge CM. Estradiol downregulates miR-21 expression and increases miR-21 target gene expression in MCF-7 breast cancer cells. Nucleic Acids Res 2009; 37:2584- 95.
56. Zhang Y, Eades G, Yao Y, Li Q, Zhou Q. Estrogen receptor α signaling regulates breast tumor-initiating cells by downregulating miR-140 which targets the transcription factor SOX2. J Biol Chem 2012; 287:41514-22. http://dx.doi.org/10.1074/jbc.M112.404871
57. Pinho FG, Frampton AE, Nunes J, Krell J, Alshaker H, Jacob J, et al. Downregulation of microRNA-515-5p by the estrogen receptor modulates sphingosine kinase 1 and breast cancer cell proliferation. Cancer Res 2013; 73:5936-48. http://dx.doi.org/10.1158/0008-5472.CAN-13-0158. 81.
58. Lee YM, Lee JY, Ho CC, Hong QS, Yu SL, Tzeng CR, et al. miRNA-34b as a tumor suppressor in estrogen-dependent growth of breast cancer cells. Breast Cancer Res 2011; 13:R116.
59. Yu X, Zhang X, Dhakal IB, Beggs M, Kadlubar S, Luo D. Induction of cell proliferation and survival genes by estradiol-repressed microRNAs in breast cancer cells. BMC Cancer 2012; 12:29.
60. Yamagata K, Fujiyama S, Ito S, Ueda T, Murata T, Naitou M, et al. Maturation of microRNA is hormonally regulated by a nuclear receptor. Mol Cell 2009; 36:340-7.
61. Di Leva G, Gasparini P, Piovan C, Ngankeu A, Garofalo M, Taccioli C, et al. MicroRNA cluster 221-222 and estrogen receptor alpha interactions in breast cancer. J Natl Cancer Inst 2010;102:706-21.
62. Qian P, Zuo Z, Wu Z, Meng X, Li G, Zhang W, et al. Pivotal role of reduced let-7g expression in breast cancer invasion and metastasis. Cancer Res 2011; 71:6463-74.
63. Paris O, Ferraro L, Grober OM, Ravo M, De Filippo MR, Giurato G, et al. Direct regulation of microRNA biogenesis and expression by estrogen receptor beta in hormone-responsive breast cancer. Oncogene 2012; 31:4196-206.
64. Edvardsson K, Nguyen-Vu T, Kalasekar SM, Pontén F, Gustafsson J, Williams C. Estrogen receptor β expression induces changes in the

microRNA pool in human colon cancer cells. Carcinogenesis 2013; 34:1431-41.
65. He YQ, Sheng JQ, Ling XL, Fu L, Jin P, Yen L, et al. Estradiol regulates miR-135b and mismatch repair gene expressions via estrogen receptor-beta in colorectal cells. Exp Mol Med 2012; 44:723-32.
66. Queiros AM, Eschen C, Fliegner D, Kararigas G, Dworatzek E, Westphal C, et al. Sex- and estrogen-dependent regulation of a miRNA network in the healthy and hypertrophied heart.Int.Jr.Cardiology2013;169:331-8.
67. Nothnick WB, Healy C. Estrogen induces distinct patterns of microRNA expression within the mouse uterus. Reprod Sci 2010;17:987-94.
68. Dai R, Phillips RA, Zhang Y, Khan D, Crasta O, Ahmed SA. Suppression of LPS-induced Interferon-gamma and nitric oxide in splenic lymphocytes by select estrogen-regulated microRNAs: a novel mechanism of immune modulation. Blood 2008;112:4591-7.
69. Bhat-Nakshatri P, Wang G, Collins NR, Thomson MJ, Geistlinger TR, Carroll JS, et al. Estradiol-regulated microRNAs control estradiol response in breast cancer cells. Nucleic Acids Res 2009;37:4850-61.
70. Masuda M, Miki Y, Hata S, Takagi K, Sakurai M, Ono K, et al. An induction of microRNA, miR-7 through estrogen treatment in breast carcinoma. J Transl Med 2012;10:S2.
71. Zhang C, Zhao J, Deng H. 17beta-estradiol up-regulates miR-155 expression and reduces TP53INP1 expression in MCF-7 breast cancer cells. Mol Cell Biochem 2013;379:201- 11.
72. Wang G, Wang Y, Shen C, Huang YW, Huang K, Huang TH, et al. RNA polymerase II binding patterns reveal genomic regions involved in microRNA gene regulation. PLoS One 2010;5:e13798.
73. Zhang R, He Y, Zhang X, Xing B, Sheng Y, Lu H, et al. Estrogen receptor-regulated microRNAs contribute to the BCL2/ BAX imbalance in endometrial adenocarcinoma and precancerous lesions. Cancer Lett 2012; 314:155-65.
74. Cochrane DR, Cittelly DM, Howe EN, Spoelstra NS, McKinsey EL, LaPara K, et al. MicroRNAs link estrogen receptor alpha status and Dicer levels in breast cancer. Horm Cancer 2010; 1:306-19.
75. Maillot G, Lacroix-Triki M, Pierredon S, Gratadou L, Schmidt S, Bénès V, et al. Widespread estrogen-dependent repression of micrornas involved in breast tumor cell growth. Cancer Res 2009; 69:8332-40.
76. Jacovetti C, Abderrahmani A, Parnaud G, Jonas JC, Peyot ML, Cornu M, et al. MicroRNAs contribute to compensatory β cell expansion during pregnancy and obesity. J Clin Invest 2012; 122:3541-51.
77. Peter Vrtačnik, Barbara Ostanek, Simona Mencej-Bedrač, Janja Marc. The many faces of estrogen signaling. Biochemia Medica 2014; 24(3):329–42