

REVIEW

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Influence of sex differences on microRNA gene regulation in disease

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Abstract

Sexual dimorphism is observed in most human diseases. The difference in the physiology and genetics between sexes can contribute tremendously to the disease prevalence, severity, and outcome. Both hormonal and genetic differences between males and females can lead to differences in gene expression patterns that can influence disease risk and course. MicroRNAs have emerged as potential regulatory molecules in all organisms. They can have a broad effect on every aspect of physiology, including embryogenesis, metabolism, and growth and development. Numerous microRNAs have been identified and elucidated to play a key role in cardiovascular diseases, as well as in neurological and autoimmune disorders. This is especially important as microRNA-based tools can be exploited as beneficial therapies for disease treatment and prevention. Sex steroid hormones as well as X-linked genes can have a considerable influence on the regulation of microRNAs. However, there are very few studies highlighting the role of microRNAs in sex biased diseases. This review attempts to summarize differentially regulated microRNAs in males versus females in different diseases and calls for more attention in this underexplored area that should set the basis for more effective therapeutic strategies for sexually dimorphic diseases.

Introduction

Many complex regulatory steps are important in the conversion and dissemination of genetic information to molecular effectors. This regulation is fine tuned by a number of transcriptional and post transcriptional mechanisms. Sex differences can have major contributions in defining the course of these regulatory steps. Whether it is the presence of a Y chromosome, an extra X chromosome or a difference in the hormonal milieu, these gender differences are remarkably reflected in the disease outcomes. Gender differences have been already highlighted in a number of diseases and disorders associated with neurodevelopment, cancers, cardiovascular and immune systems [1-10]. MicroRNAs regulate various physiological processes ranging from cell growth and differentiation to cell metabolism, development, morphogenesis, maturation and apoptosis [11-21]. The dysregulation of microRNAs and consequently of their target genes has been widely

linked to various pathologic conditions of the heart, lung and brain, as well as in many cancers [22-33]. Thus, it is worthwhile to examine their role in the context of sex differences and disease outcome.

There is a differential expression of microRNAs in males and females. This sex-biased expression of microRNAs has been observed both in invertebrates as well as in higher organisms [34-38]. The sex difference in the expression of microRNAs has also been observed in embryonic stem cell differentiation. In particular, it has been shown that miR-302 is enriched in the male embryonic stem cell differentiation and germ line determination, but not in female cells [39]. Another example is the sex-associated differential expression of microRNAs during lung development, which ultimately leads to differences in the structure and function of lungs between males and females [40]. This sex-biased difference in microRNA expression is of great biomedical interest. The contribution of differential microRNA expression in sexually dimorphic disease development has also been explored to some extent [41,42]. This review will highlight our current knowledge on the differential expression of microRNAs between genders, the sex chromosome and sex hormone-mediated regulation of microRNAs and how

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this sexually biased microRNA expression contributes to the sex differences in the disease outcome.

Review

MicroRNA biogenesis

MicroRNAs are small, non-coding, approximately 19-22-nucleotide-long RNA molecules. Their function is to regulate gene expression by mRNA degradation or to attenuate translation of their target genes. The very first identified microRNAs, *lin-4* and *let-7* were discovered in *Caenorhabditis elegans* in the early 1990s [43-45]. MicroRNAs are reported in a wide variety of organisms ranging from single-cell organisms to metazoans, plants and mammals [46-49]. In mammals, it is estimated that approximately 60% of all protein-coding genes are under microRNA regulation [50,51]. MicroRNAs are involved in the regulation of virtually all cellular processes including metabolism, development, morphogenesis, programmed cell death, angiogenesis and so on [14,21,33,52-57]. Their dysregulated expression is also associated with human pathologies, including neurological disorders, cardiovascular diseases and cancer [27,28,30].

With the help of RNA polymerase II, microRNAs are transcribed from long precursor molecules called pri-miRNA present as independent genes or in the introns of protein coding genes. Two RNA polymerase III enzymes, Droscha and Dicer, act on these hairpin pri-miRNAs. Droscha cleaves the hairpin into approximately 70 nucleotide pre-miRNA molecule, which then is exported out of the nucleus by active transport. In the cytosol, Dicer processes it to an approximately 20-bp miRNA/miRNA* duplex. One strand of this duplex represents the mature microRNA. This mature miRNA is then incorporated in a multi protein complex, the miRNA-induced silencing complex (miRISC). MicroRNA-induced translational repression is guided within miRISC. Lastly, the assembly and function of ribonucleases and miRISCs are assisted by proteins and key cofactors including argonaute proteins [43-45,58]. The regulation of microRNA biogenesis is important for the tissue- and development-specific control of microRNA expression. The sophisticated control of microRNA biogenesis, function and decay is essential, as these regulatory molecules play a fundamental role in all known cellular processes.

Sex-specific difference in microRNA expression

Hormonal and genetic differences between males and females bear considerable impact on health and disease. One particular area of interest is the microRNAs which can have broad effect on downstream signaling pathways. Differences in miRNA expression between males and females can help us further understand the biological and physiological differences between the sexes. These sex differences in microRNA expression are a

result of both hormonal and genetic differences between the sexes.

Sex hormonal regulation of microRNAs

Several sex steroid hormones, such as estradiol, progesterone and testosterone, regulate microRNA expression [58-64]. A distinct sex-specific pattern of microRNA expression in neonatal rodent brains was observed. This difference in expression almost disappeared when the conversion of testosterone to estradiol was blocked in males, suggesting that microRNAs are regulated by estrogens [65]. Sex hormones bind to nuclear hormone receptors to directly or indirectly alter gene expression. This ligand-bound nuclear hormone complex binds to the promoter elements of multiple genes, recruits coactivators or corepressors, and regulates gene transcription. MicroRNAs are either embedded in their host genes or have their own promoter elements. They are either coregulated or regulated in the same manner as their host genes. In addition, nuclear hormone receptors can regulate multiple downstream target genes. These target genes could induce or repress microRNAs as a part of a bigger molecular network [66-68]. Thus, the hormonal regulation of microRNAs could be direct as well as indirect. Another important mechanism of hormonal regulation of microRNAs is at the level of the microRNA processing machinery. There are multiple steps involved in the processing of microRNAs. The ribonucleases Droscha and Dicer are part of larger protein complexes, and play key roles in the activation or repression of these complexes to regulate microRNA maturation. Furthermore, hormones can also regulate Droscha and Dicer, thus broadly regulating microRNAs. For example, estradiol signaling has been shown to alter the expression of argonaute, Droscha and Dicer [69-73]. Thus, hormonal regulation of microRNAs can occur both directly by binding to the promoter elements of microRNAs or indirectly via regulation of post transcriptional processing proteins. This could have broad signaling effects at the molecular and cellular level.

Sex chromosomal regulation of microRNAs

Differences in the expression of microRNAs can be partly attributed to a differential regulation by sex chromosome genes. Gene expression in males and females differs since females possess two copies of the X chromosome and lack the Y chromosome. Since males are hemizygous for the X chromosome-linked genes, they are more prone to diseases associated with recessive mutations. There is a high density of microRNAs on the X chromosome. According to miRBase microRNA archive (www.miRBase.org 2013), the X chromosome encodes 113 microRNAs whereas Y chromosome encodes only 2. Many genes in the X chromosome are inactivated in order to balance the expression of most but not all X-linked genes in females and

males. Approximately 15% of genes encoded by the inactive X chromosome in humans escape inactivation [74-77], which in some cases results in higher expression of the X gene in females than in males. The inactivation status of X-linked miRNAs is not well characterized. Interestingly, the expression of sex-biased microRNAs in the neonatal brain could stem from both hormone and sex chromosome effects [78].

Sex-biased differences in microRNA expression influences disease pathogenesis

Males and females differ in disease outcome and pathogenesis. In a number of autoimmune diseases, females have higher incidence of disease than males [10,42,79,80]. In contrast, the pathogenesis of many cancers is higher in males than females [81]. The incidence of cardiovascular diseases is also higher in men than women before menopause [82,83]. Therefore, differential expression of microRNAs between the sexes may be an important underlying mechanism for gender-biased disease outcome (Table 1).

Autoimmune diseases

Autoimmunity results from the misdirected response of immune system to body's healthy cells, leading to autoimmune diseases including rheumatoid arthritis, type I diabetes and systemic lupus erythematosus [89,90]. Multiple factors, hormonal or genetic, either protect males or increase vulnerability of females [10]. Behavioral differences between the sexes could also alter susceptibility to infection [91]. The X chromosome is enriched in microRNAs and there is a possibility that microRNAs may escape X-linked inactivation [78,92]. This could result in the suppression of many microRNA-regulated target genes involved in immunosuppressive pathways, leading to a heightened autoimmune response in females

and their predisposition to autoimmune diseases [93,94]. Predisposition of women to systemic lupus erythematosus is due to overexpression of immune active genes, resulting in T cell autoreactivity. Various factors contribute to the pathogenesis of systemic lupus erythematosus. These include genetic factors such as skewed X chromosome inactivation, environmental and epigenetic factors such as DNA methylation and smoking, and hormones or microRNAs that could possibly make women more susceptible [95-97]. Interestingly, in the NZB/WF1 murine model that closely mimics human lupus, a clear sex difference in the systemic lupus erythematosus-associated microRNAs was observed. Particularly, increased expression of miR-182 cluster, miR-155, miR-31, and miR-148a was observed in female NZB/WF1 mice at an age after the onset of lupus. Administration of estrogens to castrated male NZB/WF1 mice resulted in the expression of female-associated systemic lupus erythematosus microRNAs including the miR-182 cluster, miR-379, and miR-148a, thus demonstrating the role of sex hormones in the regulation of sexual dimorphism of microRNAs [84]. In addition, estrogens are important modulators of the immune system and contribute to the gender difference in autoimmune disease susceptibility [98-100]. Estrogen treatment augments innate immune response of murine splenic lymphocytes to Lipopolysaccharide by manipulating select microRNAs, including miR146a and miR-223 [101]. Thus, estrogen-mediated regulation of microRNAs may serve as an important parameter in gender-biased disease susceptibility.

Neurodegenerative disorders

The precise temporal regulation of microRNAs is especially important in the development of the central nervous system, in which developmental events need to be

Table 1 MicroRNAs showing sex-biased expression in different pathological conditions

| Disease/development | MicroRNAs | Expression changes between males and females | Hormone regulated | Chromosome linked |
|------------------------------|---|--|-------------------|-------------------|
| Autoimmune diseases | | | | |
| Systemic lupus erythematosus | miR-182 cluster, miR-31, and miR-148a [84] | M < F | Estrogens | - |
| Neurodegenerative diseases | | | | |
| Schizophrenia | miR-30b [85] | M > F | Estrogens | |
| | let-7f-2, miR-18b, miR-505, miR-502, miR-188, miR-325, miR-660 and miR-509-3 [41] | No expression changes reported (only mutational changes between disease and control) | | X chromosome |
| Cerebral ischemia | miR-23a [37] | M < F | - | - |
| Neurodevelopment | miR-322, miR-574, and miR-873 [65] | M < F | Estrogens | - |
| Metabolic diseases | miR-221, let-7 g [86] | M < F | - | - |
| Breast cancer | miR17, let-7a [87]; miR-137 [35] | M < F M < F promoter methylation of miR-137 | - | - |
| Liver fibrosis | miR-29a, miR-29b [88] | M < F | Estrogens | - |

finely tuned. This became evident when deletion of the microRNA processing enzyme Dicer in zebrafish resulted in the disruption of neuronal differentiation [21]. MicroRNAs are involved in various neurologic processes including neuronal development (miR-430, miR-9, miR-10) [21,102-106] and neuronal cell maintenance (miR-29a/b, miR-134) [107,108]. Also, of scientific interest, is the role of microRNAs in the aging brain since there is a global downregulation of gene expression in the brain with age [109-112]. It is also well known that the functional and cognitive decline in the aging brain differs between men and women, as many neurological disorders such as Alzheimer's disease are expressed differentially between the sexes. Sex hormones and chromosomes could very well contribute to this difference [113-115]. MicroRNAs including miR-125a/b, miR-495 and miR-181 have been shown to be dysregulated in a variety of neurological disorders such as Alzheimer's disease. These microRNAs also target proteins such as β -site amyloid precursor protein-cleaving enzyme-1 that are critical in the pathology of Alzheimer's disease [116-118]. Hormonal regulation of microRNAs is attributed to neurodegenerative disorders [65]. It is also speculated that sex chromosomes could regulate microRNAs in neurodegenerative disorders [78].

The effects of ionizing radiation on the expression of microRNAs were studied in different brain regions in male and female mice. Interestingly, the number of microRNAs that showed changes in expression upon exposure to radiation was larger in females than males. Notably, the expression of miR-29a was downregulated only in the frontal cortex region of females accompanied by an increase in the protein levels of miR29a target DNMT3a, a DNA methyltransferase. It is possible that an increase in DNA methylation via miR29a downregulation serves as a protective mechanism in females against the adverse effects of radiation [34]. In contrast, only a few studies in humans have measured sex differences in microRNA expression in the brains of patients with neurological diseases such as Alzheimer's disease or schizophrenia. The levels of miR-30b were observed to be significantly downregulated in the brains of female schizophrenic patients compared to males. MiR-30b was shown to be regulated by estrogens and therefore, it is most likely under hormonal control [85]. Another relevant study specifically focused on the association of microRNAs on the X chromosome with high prevalence of schizophrenia in males compared to females. Mutations in X-linked microRNAs that can possibly predispose males to schizophrenia were identified. Some key targets identified for these microRNAs include Neuregulin-1, Disrupted in schizophrenia-1, and Regulator of G-protein signaling-4, which have been previously described as candidate genes for schizophrenia [41]. The underlying cause of cerebral ischemia differs between males and females. In males the cause of stroke-

related death is primarily due to caspase-independent mechanisms, whereas in females it involves caspase-dependent pathways [119-121]. X-linked inhibitor of apoptosis, which is the primary endogenous inhibitor of caspases, is significantly reduced in post-stroke females compared to no significant changes in males. This was attributed to the differential expression of the microRNA miR-23a in the male and female brains. Also, the X-linked inhibitor of apoptosis was characterized as the bona fide target of miR-23a, thus implicating miR23a as a candidate for sexually dimorphic diseases [37]. Many neurodevelopmental disorders including schizophrenia and autism are linked to prenatal stress [122,123]. In a murine model, early gestation was reported to be the period where male mouse embryos are most susceptible to maternal stress. As adults, these male mice showed cognitive defects typical of human neurodegenerative disease. They also showed dysmasculinization in their response to stress, as well as a female pattern of gene expression associated with neurodevelopment. The microRNA profile in these male brains included significant downregulation of miR-322, miR-574, and miR-873, showing similarity to control female brains [65]. These data further confirm the important role of microRNAs in the development of the sexually dimorphic brain.

Metabolism

Metabolic syndrome includes all the risk factors that can increase the susceptibility to, or lead to health disorders, including heart disease, type 2 diabetes, and stroke. Because of high obesity rate, metabolic syndrome is fast approaching as one of the major risk factors for heart disease [124-126]. Sex is a significant modifier for metabolic syndrome-related cardiovascular and non-cardiovascular complications. Wang *et al.* discovered that miR-221 and let-7g were expressed more prominently in the plasma of women than men manifesting metabolic syndrome [86]. This may have significant implications in the susceptibility of these women to cardiovascular risk factors. Interestingly, the expression of these microRNAs positively correlated with the increase in number of risk components associated with metabolic syndrome including high blood pressure and low HDL levels.

Cardiovascular diseases

The incidence and progression of heart disease is markedly higher in men than in age-matched women before menopause, whereas after menopause the incidence is similar or even higher in women than age-matched men [82,83]. The lower incidence and better protection of women against coronary artery disease during reproductive years is attributed to the presence of female sex hormones [127]. The protective role of estradiol has been highlighted in the context of myocardial ischemia/reperfusion injury

in women as well as females in animal models [128]. In addition, the regulation of microRNAs by estrogens and other sex hormones is well established [58-64]. However, the link between sex differences in microRNAs and their effect on the incidence and course of cardiovascular disease is largely unexplored. Future studies on this issue will help in the understanding of sex-biased difference in cardiovascular disease.

Cancer and liver disease

The dysregulation of microRNAs is implicated in the pathogenesis of many cancers. For instance, the regulation of microRNAs is involved in the progression of breast cancer. Breast cancer is prevalent among women in the western world, with much lower incidence among males [129-131]. Multiple microRNAs have dysregulated expression in breast cancer versus normal controls both in breast tissue and in blood circulation [132-135]. Of interest, Pinto *et. al.* presented a significant correlation between miR17 and let-7a frequency and regulation in familial breast cancer in women compared to men [87]. Langevin *et. al.* also show that promoter methylation of miR-137 occurs frequently in squamous cell carcinoma of the head and neck. This microRNA is implicated in cell cycle control and differentiation. This aberrant methylation shows a bias toward females and may be associated with environmental and personal risk factors [35].

Some chronic liver diseases manifest different progression rates in males versus females. For example, liver fibrosis is one of the hallmarks of chronic viral hepatitis and has a higher incidence in males than females. It is characterized by extensive deposition of collagens in the extracellular matrix [136,137]. In the carbon tetrachloride mouse model of fibrosis, females are more protected against liver fibrosis than males. This has been attributed to the induction of miR-29a and miR-29b by estrogens in females. MiR-29 family members decrease the content of collagens by directly targeting them and thus block the process of development of fibrosis [88,138].

Conclusions

In recent years, microRNAs have emerged as powerful regulatory molecules. Gain and loss of function studies in various animal models mimicking human disease have shed light on the functional role and target specification of microRNAs. However, the role of miRNAs in mediating sex biases in diseases is understudied and underappreciated. There is a plethora of literature showing sexual dimorphism in the context of neurological and autoimmunity disorders. This is attributed to both hormonal and sex chromosome differences between males and females. Estrogens have been shown to regulate a number of microRNAs in various cell studies. Similarly, the X chromosome is enriched in a number of microRNAs

involved in various physiological processes, especially immunity. Thus, it is likely that these microRNAs can influence sex-specific responses to disease prevalence, pathogenesis, and outcome. Further research in exploring the gender-specific roles of microRNAs is extremely important for the development of effective therapeutic strategies for sexually dimorphic diseases.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SS and ME drafted the manuscript. Both authors read and approved the final manuscript.

Authors' information

http://www.anes.ucla.edu/dmm/eghbali/.

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