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Review

Estrogen repression of microRNA as a potential cause of cancer

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ABSTRACT

MicroRNAs (miRNAs) are endogenous small molecules that regulate gene expression and have been implicated in the pathogenesis of many human diseases, including cancer.

This review describes the results that show a global repression in miRNA expression in various tumors and cancer cell lines. Intriguingly, recent discoveries have shown a widespread downregulation of miRNA after exposure to the steroid hormone estrogen. The integration of the results suggests that estrogen-dependent repression of miRNA is a potential cause of cancer.

Contents

1. Mechanisms of estrogen signaling

In vertebrates, estrogens, primarily 17β-estradiol (E2), regulate a large array of physiological processes such as growth, differentiation, functioning of the reproductive, skeletal, cardiovascular and central nervous systems [1,2]. In addition, E2 has also been implicated in the development of a variety of diseases such as cancer [3].

Steroid hormone receptors; including estrogen, progesterone and androgen receptors (ER, PR and AR, respectively) are ligand-activated transcription factors that share common structure domains and regulate genes in steroid responsive tissues [4]. Two main ERs (ERalpha and ERbeta) have been characterized. In the "classical" mechanism of estrogen action, E2 diffuses into the cell and binds to ERs, which are mostly located in the nucleus of target cells [5]. After ligand binding, ERs form homodimmers or heterodimmers that bind to inverted palindromic estrogen response elements (ERE) sequences in the promoter region of estrogen-responsive genes [6]. Several variations on the 13 base pairs (bp) ERE consensus sequence (GGTCAnnnTGACC) enable stable ER binding, resulting in recruitment of co-activators or co-repressors to the promoter that leads to increased or decreased mRNA levels and associated protein production and to physiological responses [7]. However, other mechanisms also exist, such as interactions of ERs with other transcription factors at AP-1 and Sp1 sites and also non-genomic estrogenic pathways mediated by cell membrane receptors which are relatively rapid and do not depend on RNA and protein synthesis [8,9]. These extranuclear responses start in membrane receptors, as the G protein-coupled receptor 30 (GPR30), insulin-like growth factor-1-receptor (IGF-1R) and epidermal growth factor receptor (EGFR) and include mobilization of second messengers, like calcium, cAMP and nitric oxide and activation of intracellular enzymes, such as Src, PI3K, AKT and MAPK [9,10].

Many studies reveal that xenoestrogens [also referred to as endocrine disrupting chemicals (EDCs) or endocrine disruptors] are a significant concern to public health and there is evidence for EDCs functioning as carcinogens (Table 1) in the development of breast and prostate cancer [11,12]. Recently, two ubiquitous EDCs, the pesticide DDT and a material used to make plastics, bisphenol A, were shown to affect microRNA (miRNA) expression in breast

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Table 1
Agents with xenoestrogenic activity and their potential health risks.

Xenoestrogen	Possible effects	Reference
Dichlorodiphenyltrichloroethane (DDT)	Breast cancer	[47]
	Testicular tumors (TGCT)	[48]
Bisphenol-A (BPA)	Breast cancer	[49]
	Prostate cancer	[50]
Phthalates (BBP, MEP, MP, DEHP)	Breast cancer	[51,52]
	Sperm DNA damage	[53]
Polychlorinated biphenyls (PCBs)	Breast cancer	[54]
	Lung cancer	[55]
	Prostate cancer	[56]
Diethylstilbestrol (DES)	Cervical and vaginal cancer	[57,58]
Metalloestrogens	Breast cancer	[59]
Styrene	Breast cancer	[60]
Polycyclic aromatic hydrocarbons (PAH)	Lung cancer	[61,62]
	Brain cancer	[63]
Cadmium	Kidney cancer	[64]
	Ovarian and testicular cancer	[65]
Arsenic	Lung and kidney cancer	[66]

cancer cells [13] and therefore suggest that miRNAs may also be used as biomarkers of exposure to environmental estrogens.

2. Estrogen regulation of miRNAs

MiRNAs are endogenous non-coding segments of RNA, 18–25 nucleotides (nt) in length, that negatively regulate gene expression at the post-transcriptional level and have a role in networking and fine-tuning gene expression in the cell [14]. The primary long transcripts (pri-miRNAs) are first processed by an RNase-III endonuclease termed Drosha and its associated binding partner Pasha (also known as DGCR8), which cut the pri-miRNAs into 70-nt stems and loop precursors (pre-miRNAs), containing the mature miRNA sequence in one of its arms and the less abundant partially complementary miRNA mature form in the other arm [15,16]. After the first processing step, pre-miRNAs are transported from the nucleus to the cytoplasm where they are processed by another endonuclease termed Dicer [17]. The result of this processing event is a double stranded RNA, where one of its strands is incorporated into the argonaute (Ago) protein of the RNA-induced silencing complex (RISC) that targets it to a 3′ untranslated region (3′UTR) of a specific mRNA and leads to its degradation or repression of translation (Fig. 1) [18].

Compelling evidence continues to accumulate that miRNAs are involved in estrogen signaling and metabolism and there are several examples of estrogen regulation of miRNAs and several

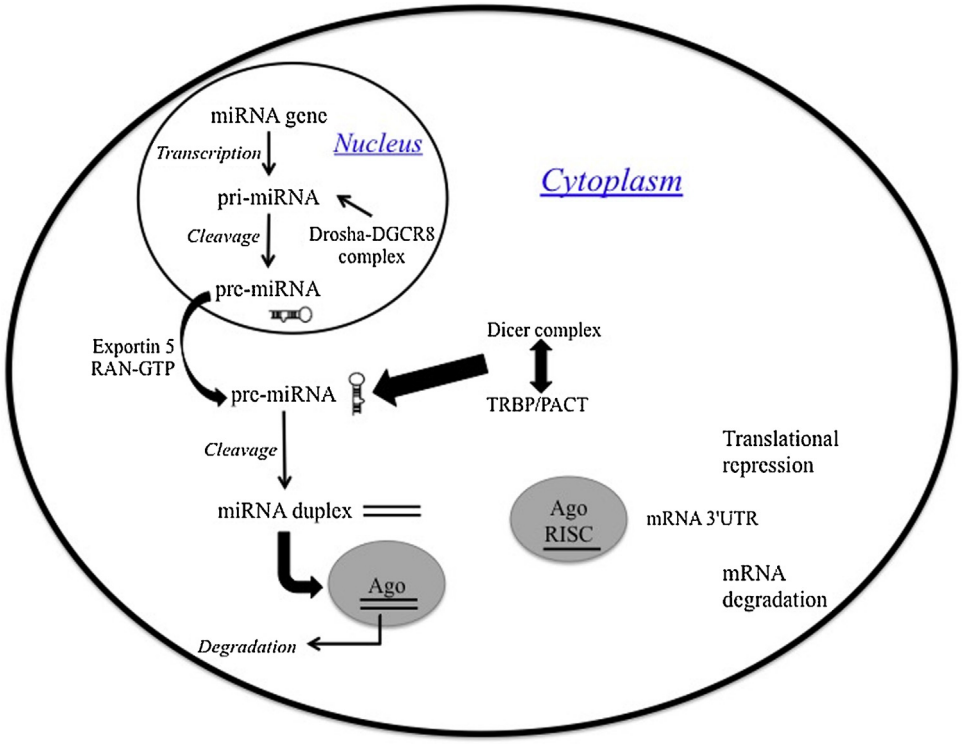

Fig. 1. Simplified microRNA biogenesis. Transcribed miRNAs by RNA polymerase II into primary-miRNAs (pri-miRNAs) are processed into precursor-miRNAs (pre-miRNAs) by the Drosha-Pasha complex (DEAD-box RNA helicases p68 and p72 DGCR8) and exported from the nucleus by Exportin/RAN-GTP to the cytoplasm. There, pre-miRNAs are processed by the Dicer complex to mature-miRNA. The RNA-binding Protein (TRBP)/Protein Activator of PKR (PACT) complex interacts with and stabilizes Dicer, and transfers miRNA to Argonaute proteins (Ago) in the RNA-induced silencing complex (RISC). miRNA guides the RISC complex to target mRNAs by binding to the 3′ untranslated region (3′UTR) of a specific mRNA and regulate posttranscriptional gene expression through various mechanisms.