

MicroRNA Regulatory Networks Provide Feedback Mechanisms for Steroid Receptor Signaling

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MicroRNAs (miRs) are short non-coding RNA molecules approximately 22-nucleotides in length that regulate gene expression through imperfect base pairing with target mRNA transcripts [1]. Primary transcripts of miRs (pri-miRs) are transcribed by RNA Polymerase II and are encoded within independent transcriptional units or within introns of protein-coding genes. Canonical miR processing begins in the nucleus where the RNase III endonuclease Drosha and DGCR8 protein complexes process miRs into stem-loop (pre-miR) molecules of approximately 70-nucleotides [1]. MiRs are exported from the nucleus to the cytoplasm by Exportin 5 proteins which recognize dsRNA, and upon reaching the cytoplasm, miRs are processed by another RNase III endonuclease, Dicer, finally resulting in a ~22-nucleotide miR duplex [2]. The mature or guide strand of this miR duplex then forms a complex with Argonaute proteins generating the RNA induced silencing complex (RISC) [2]. Once formed, this complex primarily targets the 3'un-translated region (3'UTR) and to a lesser extent the coding region or 5'UTR [3-5] of target mRNAs and results in inhibition of gene expression by cleavage of target mRNAs or inhibition of their translation [6]. Both steroid receptors (e.g., estrogen receptor, progesterone receptor) and co-regulatory proteins important in steroid receptor signaling are confirmed targets of miR regulation. Frequently, this miR-mediated regulation of steroid receptor signaling is a component of feedback mechanisms responsible for attenuating or fine-tuning steroid receptor signaling.

Estrogen receptor (ER) signaling is subject to extensive regulation by miR networks. ER α mRNA is directly targeted and repressed by multiple individual miRs including miR-206 [7], miR-221/222 [8], miR-22 [9], miR-18a/b [10], miR-145 [11], and let-7a/b/i [12]. In addition, the ER β isoform is directly targeted and suppressed by miR-92 [13]. Many of these miRs that regulate ER are involved in coordinated feedback mechanisms as a component of ER activation. Several of these ER-regulating miRs are therefore found to be estrogen-inducible, including miR-18a [14] and let-7 [15], while others are instead subject to estrogen-mediated repression, including miR-206 [7], miR-221/222 [16], and miR-145 [17]. Further complicating the relationship between miR networks and ER signaling is that ER α has also been implicated in the regulation of miR maturation. ER α was shown to associate with Drosha complex and block processing of a subset of pri-miR transcripts [18]. In addition, estrogen signaling has been shown to modulate the expression of several miR-processing enzymes including Exportin 5 [19], Dicer [19], and Argonaute 2 proteins [20].

Progesterone receptor (PR) is also subject to miR regulation. PR mRNA is directly targeted by miR-181 and miR-26a [21]. These miRs are implicated in a feed-forward loop involving ER. PR is an estrogen inducible gene whereas both miR-181 and miR-26a are estrogen-repressible genes [21]; therefore PR accumulates in response to estrogen through both transcriptional and post-transcriptional mechanisms. Another miR, miR-126-3p, is also reported to target and regulate PR mRNA [22].

MiRs are also involved in regulating other steroid receptors in addition to ER and PR. Androgen Receptor (AR) mRNA is subject to

direct targeting and suppression by numerous miRs, including miR-135b, miR-185, miR-297, miR-299-3p, miR-34a, miR-34c, miR-371-3p, miR-421, miR-449a, miR-449b, miR-634, miR-654-5p, miR-9 [23], and let-7c [24]. Similarly, glucocorticoid receptor (GR) mRNA was found to be a direct target of miR-130b [25], miR-18, and miR-124a [26]. Likewise, vitamin D receptor (VDR) mRNA is subject to direct regulation by miR-125b [27]. From these reports, it is clear that miRs are heavily involved in regulating steroid receptor signaling.

Many coregulatory proteins important in steroid receptor signaling are also subject to miR-mediated regulation. Steroid receptor coactivator 1 (SRC-1) mRNA is a direct target for miR-206 repression [28]. In addition, the coactivator Amplified in Breast Cancer 1 (AIB1) mRNA is subject to regulation by miR-17-5p [29] and miR-20a [30]. MiR suppression of steroid receptor coregulatory genes may also be a component of negative feedback from steroid receptor signaling. Both miR-17-5p and miR-20a were reportedly shown to be estrogen-inducible genes [14,15].

In addition to being the target of miR-suppression, steroid receptor signaling is also involved in regulating the expression of miRs. As briefly mentioned before, miR-221/222 are estrogen-repressible miRs [16]. In response to estrogens, ER α binds directly to the miR-221/222 promoter and recruits the corepressors Nuclear Receptor Corepressor (N-CoR) and Silencing Mediator for Retinoid and Thyroid hormone receptors (SMRT) [16]. Similarly, AR has been shown to suppress miR-221/222 expression [31]. Treatment of prostate cancer cell lines with the synthetic androgen R1881 resulted in down-regulation of miR-221/222 expression and bioinformatics analysis identified putative AR binding elements in the miR-221/222 promoter [31]. In addition, AR signaling has been shown to induce oncogenic miR-21 expression in prostate cancer cells by directly binding to the miR-21 promoter [32]. Glucocorticoids were also found to regulate miRs; dexamethasone treatment was found to induce the pro-apoptotic miR-15/16 cluster in acute lymphoblastic leukemia cells [33]. Similarly, progesterone was found to regulate miR expression. Treatment of endometrial stromal cells with the synthetic progesterone, medroxyprogesterone acetate, resulted in down-regulation of miR-20a, miR-21, and miR-26a [34]. Finally, vitamin D signaling has also been shown to alter miR expression. 1 α ,25-dihydroxyvitamin D3 treatment of colon cancer cells resulted in increased miR-22 expression, which was found to contribute to the growth suppressing properties of VDR signaling [35].

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It is clear that there is an important relationship between steroid receptor signaling and miR networks. Activation of steroid receptors may modulate miR expression through direct interactions with regulatory elements in miR gene promoters, through the actions of downstream target genes, or through modulation of miR biogenesis. In turn, miRs may regulate pathways critical for cellular response to steroid signaling or miRs may exert a regulatory effect on steroid receptors, coregulatory proteins, or steroid target genes. MiR networks are commonly involved in feedback/feed-forward loops that fine tune gene expression. It is likely that most steroid receptor signaling is robustly regulated through miR feedback pathways as has already been witnessed for estrogen receptor signaling. At an accelerated rate, research is revealing details of how steroid receptor signaling modulates miR networks and the important roles of these miRs in normal physiology and in hormone-related malignancies. Improved understanding of the connection between miRs and steroid signaling may reveal prognostic biomarkers or therapeutic targets for hormone-related cancers and other hormone-related illnesses.

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