The Role of MiRNA in the Aetiology of Polycystic Ovarian Syndrome

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1. INTRODUCTION

miRNA

MicroRNA (miRNA) are small 19 – 25 nucleotide sequences of noncoding RNA that work as an endogenous epigenetic gene expression regulators. They regulate gene expression, either decreasing mRNA stability or translation, by binding to a partially complementary 3'UTR region of their specific target mRNA. They are thought to regulate the activity of 30 – 90% genes in mammals and participate in the regulation of many cellular processes. Consequently, they play a critical role in gene regulation.

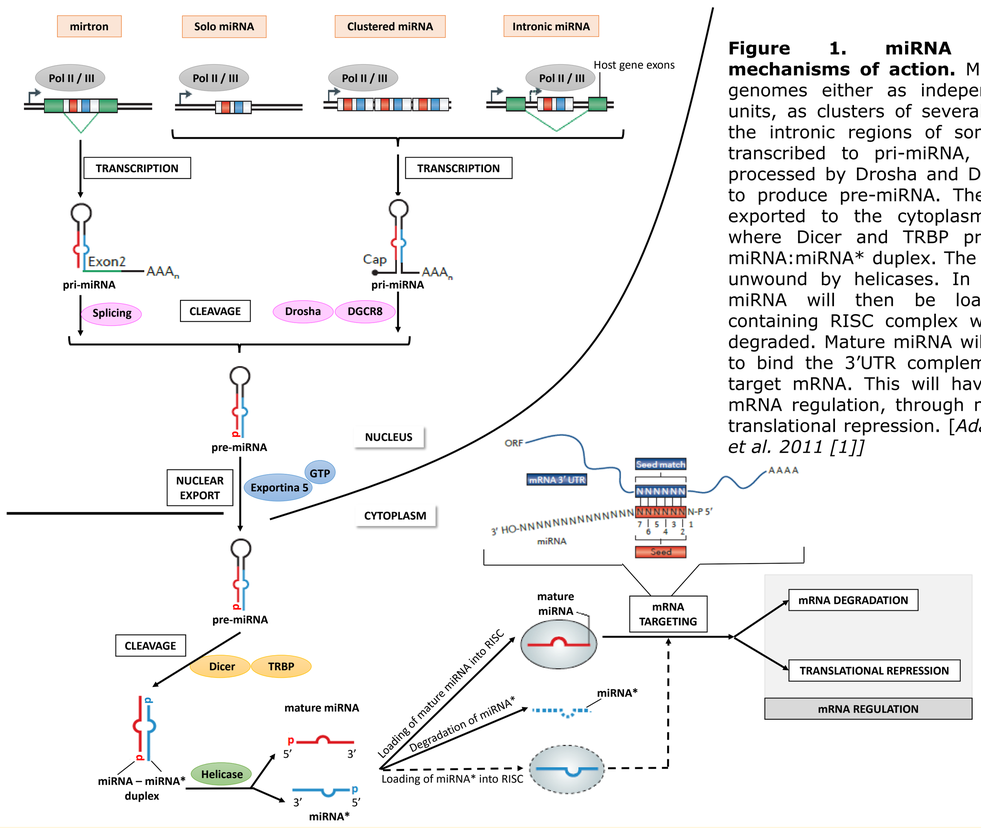


Figure 1. miRNA biogenesis and mechanisms of action. MiRNA are encoded in genomes either as independent transcriptional units, as clusters of several miRNA genes or in the intronic regions of some genes. They are transcribed to pri-miRNA, which in turn, are processed by Drosha and DGCR8 or by splicing, to produce pre-miRNA. The pre-miRNA is then exported to the cytoplasm by Exportin5/GTP, where Dicer and TRBP process it to yield a miRNA:miRNA* duplex. The double strand will be unwound by helicases. In most cases, mature miRNA will then be loaded to Argonaute-containing RISC complex while miRNA* will be degraded. Mature miRNA will be used as a guide to bind the 3'UTR complementary region of its target mRNA. This will have repercussions on mRNA regulation, through mRNA degradation or translational repression. [*Adapted from Berezikov et al. 2011 [1]*]

Polycystic Ovarian Syndrome

Polycystic Ovary Syndrome (PCOS) is the most common endocrinopathy that affect women in their reproductive age (4 – 10%) and accounts for 75% of anovulatory infertility.

It is aetiology remains unclear, although genetic and environmental factors are associated with the syndrome. It is mainly characterized by defects in folliculogenesis, leading to anovulation, and steroidogenesis. In PCOS, defects in folliculogenesis are associated with multiple cysts in the ovary, while defects in steroidogenesis cause hyperandrogenism, one of the main signs of the syndrome.

PCOS is associated with infertility and with increased risk of metabolic disorders such as diabetes, insulin resistance and obesity.

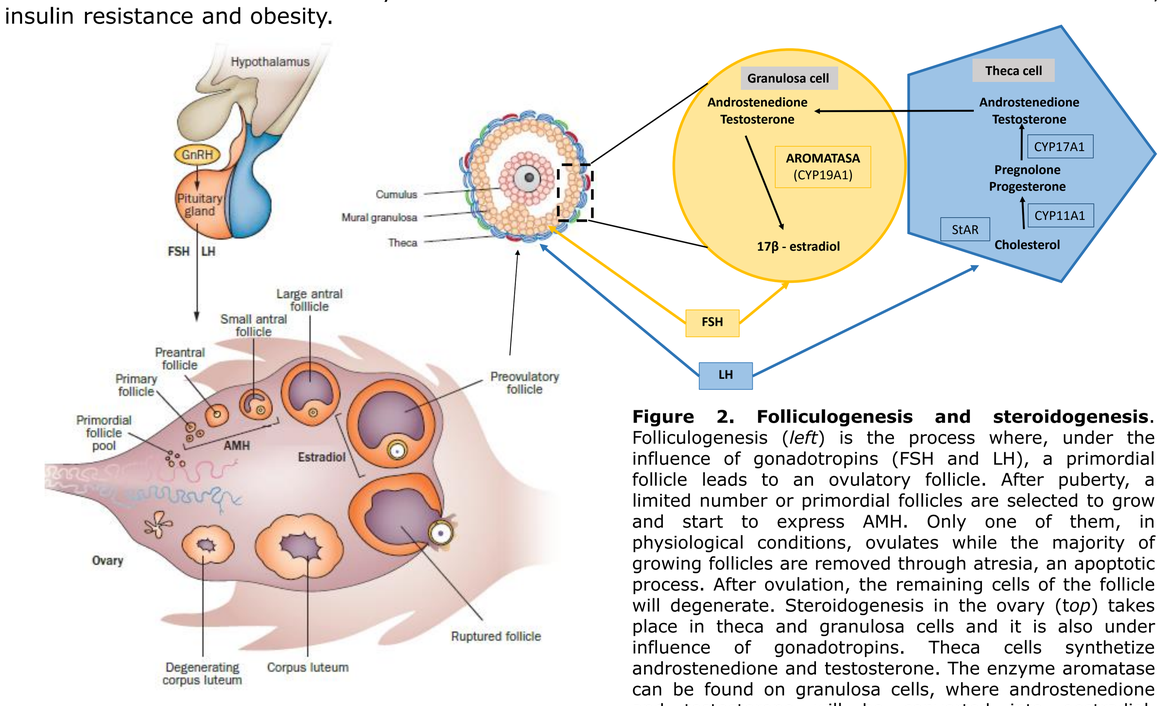


Figure 2. Folliculogenesis and steroidogenesis. Folliculogenesis (*left*) is the process where, under the influence of gonadotropins (FSH and LH), a primordial follicle leads to an ovulatory follicle. After puberty, a limited number or primordial follicles are selected to grow and start to express AMH. Only one of them, in physiological conditions, ovulates while the majority of growing follicles are removed through atresia, an apoptotic process. After ovulation, the remaining cells of the follicle will degenerate. Steroidogenesis in the ovary (*top*) takes place in theca and granulosa cells and it is also under influence of gonadotropins. Theca cells synthetize androstenedione and testosterone. The enzyme aromatase can be found on granulosa cells, where androstenedione and testosterone will be converted into oestradiol. *[Adapted from Visser et al. 2012 [2]]*

2. OBJECTIVES

The **aims** of this review are:

- To characterize the miRNA differentially expressed in granulosa and cumulus cells in PCOS patients
- To characterize the signalling pathway dysregulated by this miRNA and its biological functions
- To relate the differentially expressed levels of certain miRNA with the main affections of PCOS and its possible implications in PCOS aetiology.

3. MATERIALS AND METHODS

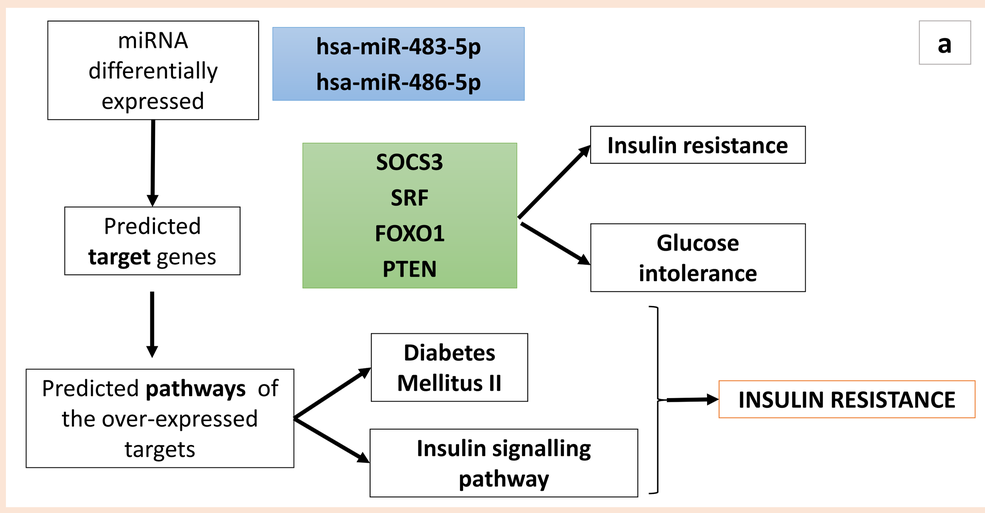
The methodology used for this review consisted on bibliographic search in PubMed in order to select the information most relevant for accomplishing the purpose of this review. Some filters were added as human specie or publication date. Publications dated on the last 13 years were consulted. Some **keywords** were used: *miRNA*, *Polycystic Ovarian Syndrome*, *granulosa cells*, *steroidogenesis*, *folliculogenesis*. Lastly, the most important articles and reviews for the project were read and synthetized.

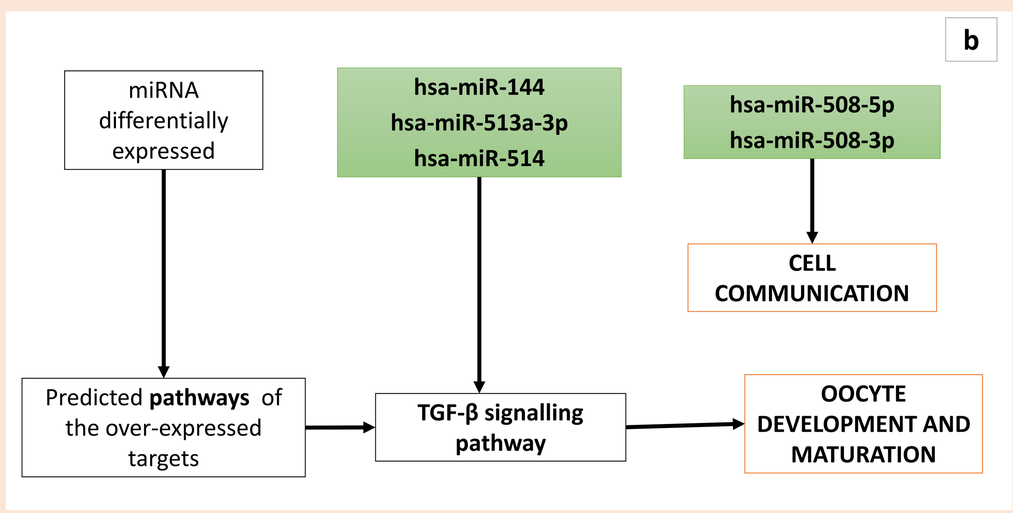
4. RESULTS

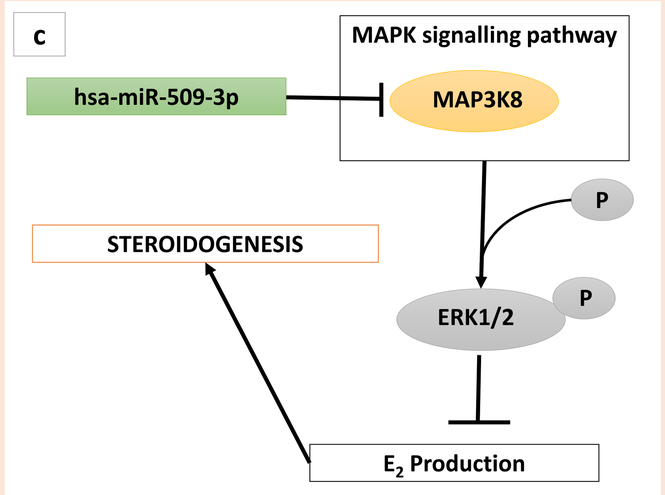
Insulin resistance, associated with PCOS, is predicted to be induced by down-regulation of hsa-miR-483-5p and hsa-miR-486-5p in cumulus cells.

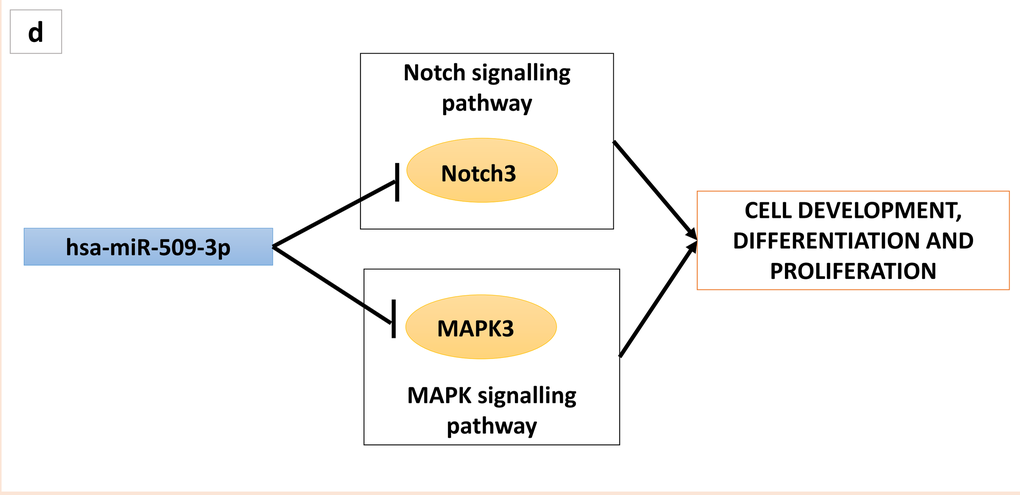
TGF-β, Notch, MAPK signalling pathway, as well as the cell cycle**,** are down or up-regulated for miRNA in granulosa cells. Known targets that have an impact on this pathways are Notch3 and MAPK3. This dysregulation leads to dysfunctions **in cell communication**, **oocyte development and maturation, cell development, differentiation and proliferation** and **G_1/S cell cycle arrest**.

MAPK signalling pathway is also the target of hsa-miR-509-3p. As this miRNA is increased in PCOS, the result of this interaction is an increased production of oestradiol that will finally entail **hyperandrogenism**.









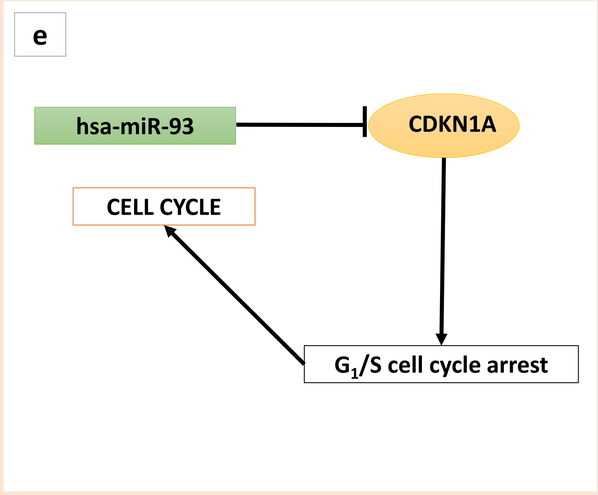


Figure 3. The role of miRNA in polycystic ovarian syndrome. (a) hsa-miR-483-5p and hsa-miR-486-5p are down-regulated in PCOS. Its predicted target genes are associated with insulin resistance and glucose intolerance. Along with the fact that the predicted pathways of the over-expressed miRNA targets are insulin signalling pathway and diabetes demonstrates hsa-miR-483-5p and hsa-miR-486-5p implication in insulin resistance. (b) hsa-miR-144, hsa-miR-513a-3p and hsa-miR-514 regulate TGF-β signalling pathway, involving this up-regulated miRNA in oocyte development and maturation. hsa-miR-508-5p and hsa-miR-508-3p play a role in cell communication. (c) MAPK signalling pathway induces ERK1/2 phosphorylation resulting in inhibition of E_2 production. Since hsa-miR-509-3p inhibit MAP3K8 and its levels are higher in PCOS, oestradiol production is increased in PCOS. (d) Notch3 and MAPK3 are targets of hsa-miR-509-3p. Notch and MAPK signalling pathway are key pathways for cell development, differentiation and proliferation. (e) Cell cycle is dysregulated in PCOS. Hsa-miR-93, up-regulated in PCOS, inhibits CDKN1A. This cyclin-dependent kinase inhibitor is essential in cell cycle and its inhibition produces G_1/S cell cycle arrest. Blue box: decreased in PCOS. Green box: increased in PCOS. Orange box: dysregulated process.

5. CONCLUSIONS

- There is evidence that miRNA are differentially expressed in polycystic ovarian syndrome (PCOS).
- The studies used for this review establish that the miRNA has a role in the aetiology of the syndrome since the pathways involved in the studied miRNA are related to it's main characteristic defects in folliculogenesis and steroidogenesis.
- Future investigations into the role of specific miRNA in PCOS will lead to a better understanding on the aetiology and the molecular mechanisms involved in PCOS.

6. REFERENCES

[1] Berezikov E. Evolution of microRNA diversity and regulation in animals. Nat Rev Genet. 2011;12(12):846–60.

[2] Visser JA, et al. Anti-Müllerian hormone: an ovarian reserve marker in primary ovarian insufficiency. Nat Rev Endocrinol. Nature; 2012;8(6):331–41.