The Role of MicroRNA in Endometriosis

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1. Introduction

MicroRNAS

MicroRNAs (miRNAs) are 22 nucleotide single stranded non-coding RNA that bind to a target mRNA, mediating translational repression or its degradation. Therefore they act like an inhibitor in the synthesis of some targeted proteins.

They play an important role in the post-transcriptional gene regulation.

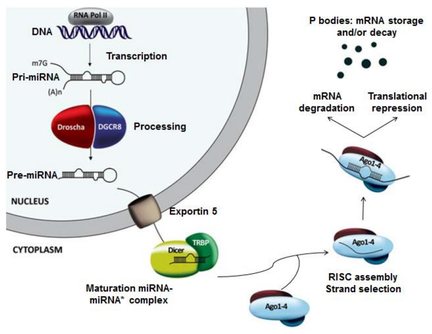

Figure 1: miRNA biosynthesis. RNA polymerase II (RNA Pol II) transcripts the primary miRNA sequence (Pri-miRNA). This one will become a precursor miRNA (pre-miRNA) by the action of Drosha and DGCR8. Thanks to exportin 5, the pre-miRNA will arrive to the cytoplasm, where it will interacts with Dicer, to finish its maturation process. This mature miRNA is assembled into the RISC complex , constituted by Argonaute proteins (Ago). With the miRNA like a guide, RISC will find the complementary mRNA and repress its translation. [Adapted from Teague et al. 2010]

Endometriosis

The endometriosis is a gynaecological disease characterized by the presence of endometrial tissue outside the uterine cavity. Its mechanism of pathogenicity and its aetiology are not known yet.
The main and the worst symptom is infertility.

About the origin of this pathology, several hypothesis have been postulated. The most accepted is the Implantation theory, this one proposes that the endometrial cells arrive to their ectopic localizations through a retrograde menstruation and they can survive there because of the immunological status of the patients.

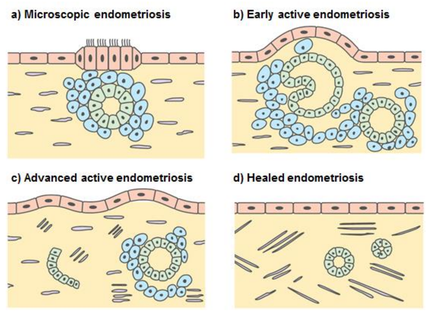

Figure 2: Evolution of the endometrial lesions. (**a**) Fist, appearance of endometrial glands in an ectopic localization. (**b**) Increase of vascularization take place. The glands become proliferative or secretor. (**c**) Glands will finally arrive to the menstrual phase. (**d**) In the end, replacement of the endometrial tissue by fibrotic tissue will heal the lesion. [Adapted from Rizk et al. 2003]

2. Materials and Methods

Scientific literature searched on Pubmed database has been selected by the publication date (from 2010 to 2015) and key words. From this database have been used reviews as well as papers.
To have a first general vision at the beginning of the research a few books were consulted.

Key words: microRNA, miRNA, endometriosis, ovary.

3. Objectives

The aim of this review is to define and illustrate the function of the miRNAs in the pathogenesis, treatment and diagnostic of the endometriosis. But to achieve this objective the concept of miRNA and endometriosis should be explained.

4. Results

The endometrium is a dynamic tissue which undergoes a cyclic series of structural changes in preparation for embryo implantation. The cycle starts with an inflammatory reaction, which degrades the tissue, followed by rapid proliferation, angiogenesis, differentiation and tissue remodeling. Studies have shown the involvement of microRNAs in controlling the above processes, which are necessary for the physiological regeneration of the endometrium after each menstrual cycle.

Hypoxia and Angiogenesis

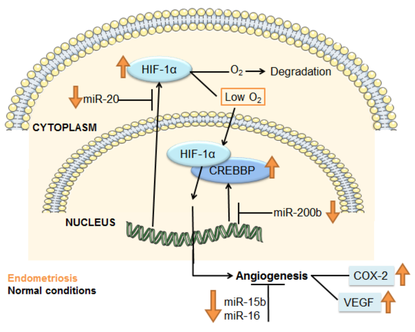

Figure 3: HIF-1α pathway in endometriotic lesions. HIF-1α (hypoxia inducible factor 1, alfa subunit), CREBBP (CREB binding protein), COX-2 (cyclooxigenase 2), VEGF (vascular endothelial growth factor).

Under lack of oxygen, HIF-α join CREBBP and lead the transcription of pro-angiogenic factors such as VEGF and COX-2 to restore the arrival of oxygen to the cells so they can continue developing. This process take place in the endometrial cells implanted in ectopic locations, and is promoted by the loss of expression of certain miRNAs.

Another mechanism that enhances angiogenesis is the overexpression of IGF-2 in endothelial cells, because it causes their proliferation and the creation of new blood vessels.

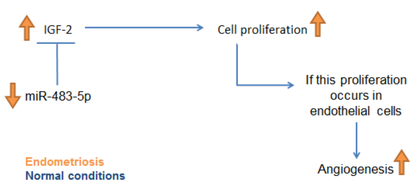

Figure 4: IGF-2 promotes angiogenesis in patients with endometriosis due to their low expression of miR-483-5p.

Inflammation

The inflammatory response is increased in endometriosis, due to the down-expression of several miRNAs.

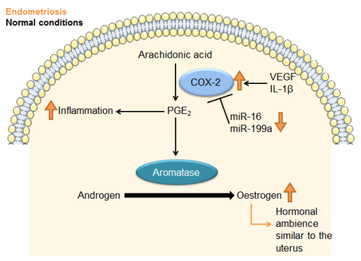

Figure 5: Up-regulation of COX-2 in endometriosis. The decreased expression of miR-16 and miR-199a will rise the translation of COX-2, that will produce inflammation and oestrogens synthesis

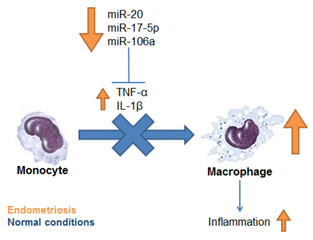

Figure 6: Monocytes differentiation. In endometriosis, the expression of the miRNAs that regulate this differentiation is inhibited, facilitating the appearance of macrophages, which potentiate the inflammatory response.

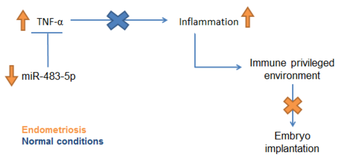

Figure 7: Uterus immune privileged environment disrupted in endometriosis. A dysregulation in the suppression of the inflammatory response in the uterus produces difficulties in the embryo implantation.

Cell Survival

Bcl-2 is one of the most important apoptosis inhibitors. The translation of its mRNA is regulated by two miRNAs (miR-15 and miR-16b), which in the case of endometriosis are poorly expressed. Therefore endometriotic lesions present high levels of Bcl-2 that provide them apoptosis resistance, enhancing the cell survival.

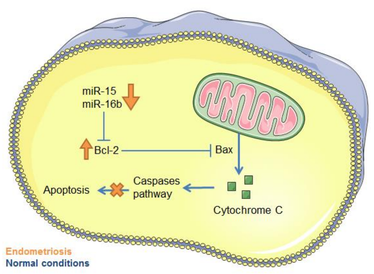

Figure 8: Role of Bcl-2 in apoptosis.

Furthermore, the cell proliferation is repressed by the hyperactivity of the cell cycle inhibitors, as explains the diagram below.

Figure 9: miRNA regulation of cell cycle inhibitors.

Extracellular Matrix Remodelling

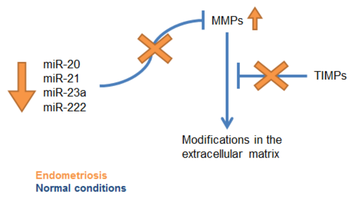

Figure 10: Extracellular matrix remodelling process. MMPs (matrix metalloproteinases), TIMPs (tissue inhibitor of MMPs).

In normal conditions, the expression of MPPs is inhibited by miRNAs, while its proteolytic action is supressed by TIMPs. However in endometriosis, the expression levels of those miRNAs are decreased, and then MMPs translation takes place, consequently the protein levels increase and act modifying the extracellular matrix.

Tissue Repair

The peritoneal fluid of endometriosis patients has several alterations. The main one is the increased levels of TGF-β. The cause of this rise is, in one hand, the low expression of miR-21 and miR-141, that produces higher rate of TGF-β translation. And on the other hand, the overexpression of miR-1 and miR-194 block TGIF mRNA, resulting in a elevated activity of TGF-β (cellular differentiation).

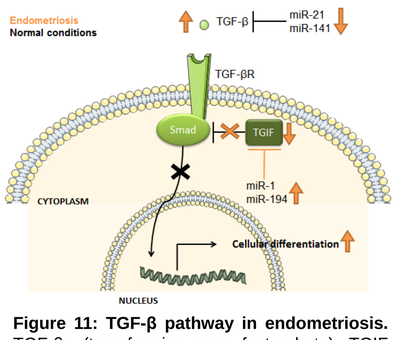

Figure 11: TGF-β pathway in endometriosis. TGF-β (transforming grow factor beta), TGIF (transforming growth factor beta induced factor).

5. Conclusions

- The relevance of microRNAs in the cellular mechanisms is increasing as the research advances. They are emerging as important regulators of diverse physiological and pathological processes.
- The alteration of miRNA expression profile could be the origin of a large number of pathologies.
- In this work, some of the miRNAs involved in the endometriosis' pathogenesis are explained , but they are not the only ones which take part in this disease, the small molecules of RNA studied so far are plentiful.
- Given that the discovery of these molecules is relatively recent, their involvement in all the pathways described have not been fully demonstrated.

6. References

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