Chapter 2

Signaling Pathways Related to Nerve Growth Factor and miRNAs in Epithelial Ovarian Cancer

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Abstract

Epithelial ovarian cancer (EOC) is a disease that causes 140,000 deaths every year. Nerve growth factor (NGF) and its high affinity receptor TRKA play important roles in follicular maturation, follicle-stimulating hormone (FSH) receptor acquisition and ovulation in normal ovary. Also, NGF has many roles in EOC cells: increasing survival, proliferation, cyclooxigenase-2 (COX-2), vascular endothelial growth factor (VEGF) and metalloproteinase ADAM17 expression. Besides, NGF inhibits calreticulin translocation from the endoplasmic reticulum to cell surface, possibly diminishing the efficacy of immunogenic therapies in EOC. Additionally, NGF acts as an angiogenic factor by a direct stimulation of migration, differentiation and proliferation of endothelial cells. Among the numerous factors actually described to be important in many types of cancer, including EOC, are the microRNAs (miRs). Indeed, it has been found that miR-143 is downregulate in EOC, which correlates with an increase of COX-2; concomitantly, NGF increases COX-2 as mentioned. Furthermore, NGF increases miR-222 and its target is the metalloproteinase inhibitor TIMP3, increasing the ADAM17 function. Also, NGF increases cMYC transcription factor in EOC, which decreases miR-23 levels regulating proteins involved in cell cycle and tumor growth. Therefore, NGF/TRKA signaling pathways alter the expression of many proteins and deregulate miRs in EOC, leading to the progression of this cancer.

Keywords: epithelial ovarian cancer, nerve growth factor, vascular endothelial growth factor, ciclooxigenasa-2, prostaglandin-E2, calreticulin, c-MYC, DAM17, microRNAs

1. Introduction

Ovarian cancer is a deadly disease that causes around 225,000 new cases and 140,000 deaths every year, remaining a major health problem worldwide [1]. Moreover, epithelial ovarian cancer (EOC) is more common in elderly women who are no longer experiencing reproductive cycles [1]. This cancer is characterized by the non-specificity of its symptoms and the lack of efficacy for therapies at advanced stages. Therefore, EOC is diagnosed at late stages and has a low overall 5-year survival below 45% [2].

A key process for EOC growth and metastasis is angiogenesis, the formation of new blood vessels from pre-existing vasculature. It is a complex process regulated by the balance between pro- and anti-angiogenic factors [3]. In the normal reproductive ovary, angiogenesis is a physiological process that occurs during every cycle in a controlled manner [4]. In cancer, pro-angiogenic factors are overexpressed and angiogenic regulation is lost. Among these factors, neurotrophins have an important role in controlling angiogenesis in the normal and neoplastic ovary, being also implicated in the regulation of other physiological and pathological processes [5]. The roles of neurotrophins in the normal ovary and in EOC are discussed in the next sections.

2. Roles of nerve growth factor in the normal ovary and in epithelial ovarian cancer

Neurotrophins are small polypeptides that were first discovered as a growth factor on the nervous system, subsequently named nerve growth factor (NGF) [6]. Besides NGF, there are four other neurotrophins: brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), neurotrophin 4/5 (NT-4/5) and neurotrophin 6 (NT-6). Besides the nervous system, most of these peptides are also found in several other systems and organs, including the ovary [7].

To induce a biological effect, neurotrophins need to interact with cell-surface receptors. All neurotrophins interact with two different types of receptors: the p75 neurotrophin receptor ($p75^{NTR}$) and a member of the tyrosine receptor kinase (TRK) family. All neurotrophins can bind to $p75^{NTR}$ with low affinity, but every different TRK receptor can bind to a specific neurotrophin with high affinity [8]. The TRK family is constituted by three members: TRKA, TRKB and TRKC. NGF binds to TRKA; BDNF and NT4/5 bind to TRKB; and NT-3 binds to TRKC. Moreover, alternative splicing can generate different TRK isoforms and some of them can initiate signal transduction pathways [9]. On the other hand, $p75^{NTR}$ and also TRK receptors can dimerize, forming either homodimers or interacting with each other (heterodimers) [10].

Nerve growth factor can induce cell survival on several systems, including the nervous, cardiovascular, immune, endocrine and reproductive systems [7]. Upon binding to TRKA, the receptor homodimerizes and autophosphorylates its tyrosine residues, inducing signaling pathways that induce trophic and anti-apoptotic effects [11]; NGF deficiency, conversely, activates apoptosis (**Figure 1**) [12]. The NGF/$p75^{NTR}$ pathway can lead to proliferation, survival or

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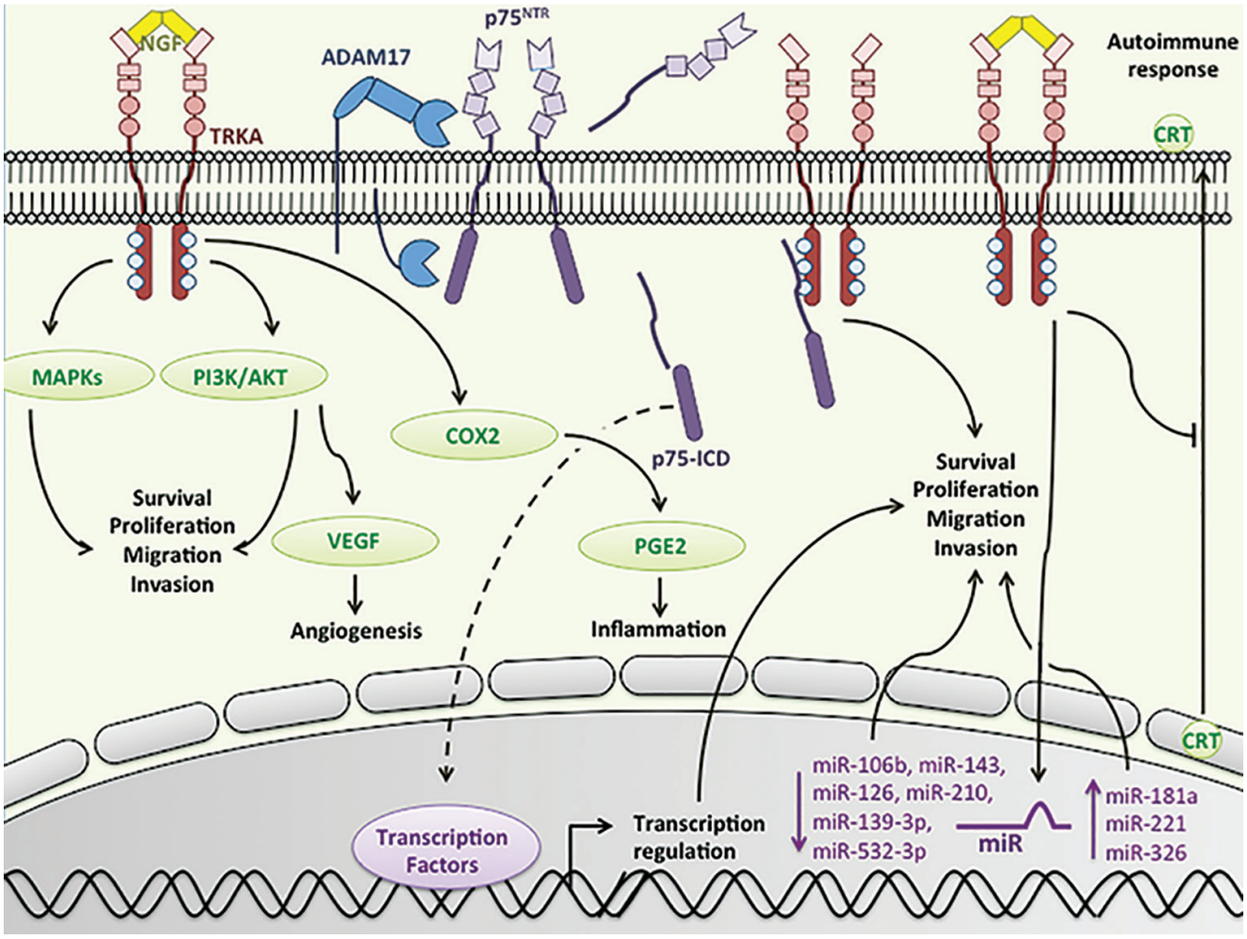

Figure 1. Several NGF-related signaling pathways are involved in epithelial ovarian cancer. NGF, a protein whose levels are elevated in EOC, activates several signaling pathways leading to carcinogenesis. Upon binding to its high affinity receptor, TRKA, NGF activates the MAPKs and PI3K/Akt signaling pathways, inducing cell survival, proliferation, migration and invasion. Through TRKA activation, NGF also increases VEGF, COX-2 and PGE 2 levels, which promotes angiogenesis and inflammation, respectively. Besides, NGF inhibits CRT translocation from the endoplasmic reticulum to the cell surface, potentially inhibiting anticancer immune responses. NGF's low affinity receptor, $p75^{NTR}$, is also present in ovarian cancer cells. This receptor can be cleaved by ADAM17, a cell surface metalloproteinase, producing an intracellular domain (p75-ICD) that could be responsible for the regulation of different processes through transcription control. Furthermore, p75-ICD can interact with TRKA, increasing its activity. Several microRNAs (miRNAs) are regulated by NGF, and these miRNAs could be responsible for NGF-mediated effects.

cell death, depending on the cell context, availability of adaptors and expression of co-receptors. While NGF can trigger apoptosis through the activation of the Jun N-terminal Kinase (JNK)/c-Jun death pathway, it can also activate the canonical NFκB signaling cascade, which promotes cell survival by increasing anti-apoptotic molecules levels [13]. The receptor $p75^{NTR}$ can also enhance TRKA phosphorylation by increasing the TRKA ability to bind to NGF [14].

Neurotrophins are involved in normal ovarian development and functioning, regulating follicular assembly, folliculogenesis and ovulation. Concerning ovarian development, $p75^{NTR}$ is expressed in the stromal cells surrounding the oocytes of human fetuses previously and during follicular assembly [15]. NGF and TRKA also seem to be necessary for follicular assembly, because mutations on these genes reduce the number of primordial follicles in mice [16].

Besides, NGF increases follicle-stimulating hormone receptor (FSHR) protein levels and the ovary response to FSH, collaborating in the growth of pre-antral follicles of 2-day-old rat ovaries [17]. Neurotrophins also participate in folliculogenesis, since they are involved in the differentiation of primordial follicles into primary follicles and in the development of secondary follicles from primary follicles [18].

In humans, NGF is present in the oocyte and granulosa cells from follicles at primordial and secondary stages, suggesting that NGF is necessary for follicle maturation after the primordial stage [16]. $p75^{NTR}$, on the other hand, is not detected on human stromal cells after birth, but theca cells from growing follicles do express this protein [15]. Concerning TRKA, this receptor is found in granulosa cells and oocytes of neonatal mice ovaries; its expression is higher on primary follicles and diminishes with folliculogenesis [15].

In human antral follicles, both granulosa and theca cells express NGF and TRKA. Furthermore, NGF has a role in ovulation, since in human ovarian granulosa cells, NGF increases FSHR and estradiol secretion [19]. Nerve growth factor contributes to ovulation by decreasing gap junctions, stimulating the proliferation of theca cells and inducing the release of prostaglandin E2 (PGE2), which acts on granulosa cells and is necessary for successful ovulation [20, 21]. Indeed, PGE2 is a paracrine mediator of luteinizing hormone (LH), and LH induces an increase of intrafollicular levels of PGE2, controlling key molecular events of ovulation, including the facilitation of follicle rupture and the release of the oocyte [22].

Angiogenesis is a key process in the normal ovarian functioning, necessary for the growth of ovarian follicles and the development and maintenance of the corpus luteum [22]. The expression and secretion of the vascular endothelial growth factor (VEGF), an important proangiogenic molecule, is key for normal adult reproductive function, and its expression is induced by the activation of FSHR and the LH receptor (LHR) [23]. VEGF production is also stimulated by NGF in cultures of human granulosa cells through the MAPK and PI3K/AKT signaling pathways [23]. Besides, NGF can directly regulate angiogenesis by acting on endothelial cells [24]. Thus, NGF participates in normal ovarian angiogenesis through its high affinity receptor TRKA.

While NGF plays a physiological role in the ovary, regulating its development and ovulation, it can also participate in cancer-related processes, particularly through its TRKA receptor [25], as seen in **Figure 1**. In cancer cells, these pathways are linked to proliferation, survival, migration and invasiveness. Interestingly, whilst in normal epithelial ovarian cells NGF and TRKA expression is only found on a small percentage of cells, both of these proteins are present in EOC tissues [26]. The active or phosphorylated form of TRKA is highly elevated in EOC compared to normal tissues, making it a possible marker for poor prognosis [27].

The NGF/TRKA signaling pathway has also been linked to several transduction cascades that stimulate cancer progression, including VEGF production and secretion [26], the COX2/PGE2 inflammatory response [28], ADAM17 activity [29] and alterations on calreticulin (CRT) subcellular localization [30]. All the molecules mentioned above have a role in the development or progression of ovarian cancer by altering processes such as inflammation, angiogenesis, immune evasion, survival and metastasis.

Angiogenesis is a vital process necessary for solid tumors to grow, develop and metastasize [31]. Several molecules are known to promote angiogenesis, in several cancer tissues including EOC; however, VEGF is considered the main angiogenic factor [32]. Its expression is controlled by the hypoxia-inducing factor (HIF-1α), a transcription factor that is produced in cells with low oxygen levels, a condition typically found on cancer cells from solid tumors [33]. VEGF induces angiogenesis by binding to its tyrosine kinase receptors located on the surface of endothelial cells, promoting their proliferation, migration and increasing their permeability [34]. In EOC explants, NGF induces an increase of VEGF levels through TRKA activation, increasing VEGF secretion [26]. Also, the NGF-conditioned medium secreted by EOC explants and by A2780 cells (an immortalized EOC cell line) induces proliferation, migration and differentiation of human endothelial Eahy926 cells [27]. Importantly, NGF, total TRKA and p-TRKA molecules are present in endothelial cells from cancer tissues. Therefore, NGF acts on EOC cells by inducing VEGF expression, besides its direct angiogenic effect by acting on the TRKA receptor found on endothelial cells [26, 35].

Moreover, given the role of NGF in the promotion of ovulation through the increase of PGE2, this neurotrophin has been linked to pro-inflammatory responses in the ovary. Interestingly, cancer has been linked to chronic inflammation, since different inflammatory pathways are activated in tumor tissues, including pathways involving cyclooxygenase (COX) proteins [36]. PGE2 is synthesized by members of the COX family: COX-1 and COX-2 [37]. COX-2 expression is inducible by external stimuli, and several molecules found in cancer, including cytokines, growth factors, oncogenes and chemicals, can induce its expression [37]. As for PGE2, this prostaglandin induces cell growth, angiogenesis, invasiveness, inhibition of apoptosis and inflammation [38]. Importantly, non-steroidal anti-inflammatory drugs (NSAIDs), which act by selectively binding to COX-1 or COX-2 and inhibiting the arachidonic acid pathway, have preventive and inhibitory effects on carcinogenesis, highlighting the importance of COX-2 in cancer [39]. Moreover, COX-2 levels have been found to be elevated in several types of cancer, including colon, gastric, breast, pancreatic, bladder and prostate cancer [40]. Therefore, COX-2 has become a focus for cancer research as a potential therapeutic target [41].

In EOC, COX-2 levels have been found to be elevated in human ovarian cancer samples compared to normal ovaries [28]. In theca cells from bovine ovaries, NFG increases COX-2 and PGE2 levels [42] and on prostate cancer cell lines, PGE2 promotes VEGF secretion [43]. Therefore, our research group explored a possible connection between NGF, COX-2, PGE2 and VEGF. In vitro experiments on A2780 epithelial ovarian cancer cells showed that NGF induces COX-2 expression and increases PGE2 levels, suggesting that NGF could stimulate inflammatory processes [28].

Other proteins that are involved in inflammatory responses are metalloproteinases, including a disintegrin and metalloproteinase domain-containing protein 17 (ADAM17) [44]. ADAM17 is expressed in granulosa cells, being important in ovary signaling during oocyte development and follicular fate determination [45].

ADAM17 is ubiquitously expressed; it is primarily active during inflammation and in cancer tissues; therefore, ADAM17 has become another focus for cancer research [46]. In lung cancer, for instance, ADAM17 protein levels are increased, and ADAM17 inhibitors aid cancer

treatment when the tumor has developed resistance mechanisms [47]. In breast cancer, ADAM17 protein levels are also overexpressed, which has been linked to tumor progression and metastasis [48]. Additionally, ADAM17 levels and activity have also been found to be elevated in colorectal, pancreatic, kidney, prostate and ovarian cancer [46].

An important ADAM17 target is TRKA, where its dimerization with $p75^{NTR}$ favors ADAM17 activation, which in turn induces $p75^{NTR}$ cleavage [49] through γ-secretase, resulting in a cytoplasmic fragment (p75-ICD) that can bind to the intracellular domain of TRKA, increasing TRKA signaling activity [50]. In human ovarian cancer samples, $p75^{NTR}$ levels are lower compared to normal ovarian tissues. In A2780 cells, ADAM17 cleaves $p75^{NTR}$, possibly decreasing p75 anticancer effects. The p75-ICD, on the other hand, increases TRKA activation, potentially inducing pro-carcinogenic processes. Besides, NGF stimulation activates TRKA, ADAM17 and γ-secretase, reducing $p75^{NTR}$ levels and increasing p75-CTF and p75-ICD levels, favoring cell survival [29]. Also, there is evidence that suggests that p75-ICD could act as a transcription regulator, enhancing TRKA cancer activity [51].

2.1. NGF effect on calreticulin subcellular localization: potential consequences for immunotherapy

Cancer cells are exposed to higher levels of endoplasmic reticulum (ER) stress, since they are exposed to stressful conditions such as hypoxia, nutrient deprivation and pH changes, among others [52]. In order to adjust to these changes, cancer cells activate the unfolded protein response (UPR), composed of three branches initiated by three proteins: IRE1α, PERK and ATF6 and sensors of ER stress [53]. In this context, calreticulin (CRT), a chaperone resident of the endoplasmic reticulum, plays a role in the adaptation of cancer cells to changes in the microenvironment [54]. CRT, a multifunctional, buffering and ubiquitous protein, is mainly involved in protein folding and the maintenance of calcium homeostasis; as a chaperone, CRT participates in protein folding quality control [54]. Under conditions of ER stress, calreticulin levels increase to restore the cell to homeostasis [55]. CRT protein levels are elevated in different cancer tissues, including EOC [37, 65], and while this increase could be associated with an adaptation to ER stress, CRT expression has also been linked to proliferation, metastasis, invasion and angiogenesis [56]. Moreover, in EOC cells, NGF induces an increase of CRT levels, which could be associated with the acquirement of carcinogenic properties [30, 57].

Importantly, despite the pro-carcinogenic effects of CRT, when this protein is found in the cell surface it can induce an anti-immune response against cancer cells [58]. In human ovarian cancer cells, our research group found that mitoxantrone, a direct ER stress inducer, can trigger CRT translocation from the ER to the cell surface [30]. Previous studies have shown that ER stress is a necessary step for CRT transport to the cell surface, and concordantly, in EOC cells, CRT translocation was accompanied by activation of the UPR protein PERK and its substrate eIF2α [59].

Interestingly, several reports show that NGF can inhibit the effects of ER stress, which could hinder cells' ability to translocate CRT from the ER to the cell surface [60–62]. Indeed, when A2780 cells were incubated with both NGF and mitoxantrone, CRT levels on the cell surface were diminished compared to cells stimulated with mitoxantrone alone [30]. Therefore, an

anticancer immune therapy based on drugs that induce CRT translocation from the ER to the cell surface could have limited efficiency in ovarian cancer patients, since NGF levels inhibit CRT translocation.

As described above in EOC, NGF is involved in many processes such as cellular survival, proliferation, angiogenesis and response to therapy. NGF could be regulating these processes through microRNA modulation; therefore, it is important to describe the role of microRNAs in EOC and its relation with NGF.

3. Role of microRNAs (miRs) in the progression of ovarian cancer and their relation with nerve growth factor

New targets of NGF and its receptor TRKA include various microRNAs (miRs). Since the 1990s, deregulation of miRs has become important in several pathological processes, including several types of cancer [63]. Currently, miRs could be used as new biomarkers and/or for therapy in various diseases [64]. Particularly in ovarian cancer some miRs are downregulated or upregulated [65], and NGF and its receptor TRKA could be implicated in the deregulation of some miRs.

MicroRNAs are the biggest family of non-coding RNAs; they are ~22-nucleotides (nts) long and regulate mRNAs post-transcriptionally [66]. The first step on miR biogenesis is the synthesis of a long primary miR (pri-miR) by an RNA polymerase II. Then, the pri-miR is cleaved, producing a pre-miR [67] that is transported to the cytoplasm to be enzymatically cleaved in its loop structure, releasing a double-strand miR called duplex [68]. This duplex has two strands, one called "mature" or "guide" miR and the other named "passenger", which is released and degraded [69]. Mature miR has ~22 nts and binds to the three-prime untranslated region (3'-UTR) of a target mRNA in order to regulate protein expression. This regulation depends on miR-mRNA complementary: total complementarity of miR with its mRNA target is a signal to cleave or degrade the mRNA. On the other hand, partial complementarily induces deadenylation of the mRNA target (facilitating its degradation) or inhibition of its translation [70]. In normal cells, microRNAs have an important role maintaining their normal functioning; however, a deregulation in their expression can lead to cellular alterations. Most studies concerning miR roles in pathologies evaluate whether there are changes on miR expression; therefore, miR targets are still being described. Regarding these targets, one miR has several targets, meaning that one miR can be involved in the development of different pathologies.

Cancer development involves miR deregulation. Cancer-related miRs are divided in two groups: oncogenic (oncomiR) and tumor suppressor (oncosuppressor) miRs; oncomirs regulate the mRNA of tumor suppressor genes, while oncosuppressors control the mRNA of oncogenes. Both of these types of miRs are normally in equilibrium; however, during carcinogenesis, they exhibit a deregulation on their expression [71]. One miR can regulate the same mRNA targets in different types of cancer, which makes them an attractive target for the development of new therapies.

Besides their potential as therapeutic targets, currently, miRs' profiles are being described in order to obtain more accurate and reliable biomarkers for cancer development and/or progression [64]; in EOC, several miRs have been found to be upregulated [72].

Interestingly, it has been found that eight miRs could be regulating 89% of the miR-associated genes [73]. Thus, to produce a more accurate clinical diagnosis, it would be beneficial to have miR profiles as biological markers.

EOC development and progression is regulated by several miRs. OncomiRs and tumor suppressor miRs modulate different processes of the hallmarks of cancer, such as proliferation, angiogenesis, migration, invasion, survival and apoptosis, among others (**Table 1** summarizes the most important miRs involved in different cancers, including EOC).

As discussed above, NGF is overexpressed in EOC and it has a significant role in the progression of this disease [35]. Interestingly, studies show that NGF could regulate the expression of some miRs. Most of these studies have been done in PC12 cells: in these cells, NGF stimulation increases the expression of several miRs [74].

Importantly, in EOC, miR-143 is downregulated [75], which is correlated with an increase of COX-2 levels [76]. As stated in the previous section, NGF increases COX-2 levels [28]. It also decreases the expression of miR-143 in PC12 cells [74]. Therefore, in EOC, the NGF-mediated COX-2 increase could be regulated through miR-143. Another miR regulated by NGF is miR-222 [77], which targets a metalloproteinase inhibitor (TIMP3) [78]. TIMP3 inhibits ADAM17 function [79]; then, NGF could increase miR-222 in order to decrease TIMP3 levels, allowing the ADAM17 activity. Consequently, NGF regulation of miR-143 and miR-222 could be important for EOC development, through the regulation of COX-2 levels and ADAM17 activity, respectively (summarized in **Table 2**).

miR	Regulation	Cancer	Targets	References
Let-7 family	↓	Lung, hepatocellular, breast and ovarian	RAS, HMGA2, cyclin D2, c-myc	[83–86]
miR-17-92	↑	Myeloma, breast, gastric and colon cancer	BIM, E2F1 PTEN	[85, 87–89]
miR-21	↑	Oral, colon, breast, glioma, ovarian and cervical cancer	PTEN, DKK2, PDCD4, TGFbR2	[85, 90–93]
miR-23a/b	↓	Colon, pancreatic and ovarian cancer	MAP3K1, Cyclin G1, RRAS2, TGFβR2	[72, 82, 94, 95]
miR-122	↓	Hepatocellular cancer	Wnt1, TCF4, Cyclin G1, B-catenin	[84, 96]
miR-143	↓	Gastric cancer	COX2	[97]
miR-125 family	↑	Renal cell carcinoma, endometrial and breast cancer	ERBB2, P53INP1, HDAC5	[85, 98–100]
	↓	Ovarian cancer	SET	[101]

One miR can be deregulated in different types of cancer; simultaneously, several miRs can be deregulated in one type of cancer. Some examples are described in the table, including oncomiRs and tumor suppressor miRs. miRs can have a dual role. A few of their mRNA targets are also depicted.

Table 1. List of miRs and some of their targets de-regulated in cancer.

NGF-related miR	Regulation	Cancer	References
miR-92a	↑	Neuroblastoma	[102]
miR-21	↑	Pheocromocitoma	[103]
miR-221/222	↑	Pheocromocitoma	[77]
miR-23b	↓	Ovarian cancer	[80]
miR-143	↓	Pheocromocitoma	[75, 76]

NGF stimulation regulates miRs in these cancers through the upregulation of several miRs, including miR-92a, miR-21 and miR-221/222, while it downregulates other miRs, such as miR-23b and miR-143.

Table 2. List of miRs regulated by NGF.

Besides, in EOC, an increase of NGF levels induces the expression of c-MYC transcription factor [80], and c-MYC downregulates the miR-23b expression [81]. This miR levels decrease in EOC, and we described that after NGF stimulation, EOC cells diminish miR-23b levels [80]. Therefore, in this cancer, NGF could reduce miR-23b levels through c-Myc. miR-23b targets cell cycle and tumor growth proteins, regulating cyclin-G1 [82] and SP-1 transcription factor [81], respectively.

4. Conclusion

Solid scientific evidences indicate that NGF has important roles in the progression of EOC by promoting the expression or activation of several proteins involved in the different carcinogenic processes, including cell proliferation, angiogenesis and in therapy resistance. For instance, NGF interaction with its TRKA receptor can activate AKT and ERK signaling, promoting cell proliferation and survival. TRKA activation by NGF also increases COX-2 and PGE2 levels, contributing to inflammatory processes, which are important to cancer progression. Besides, NGF can act on the ADAM17 metalloproteinase, which cuts the $p75^{NTR}$ receptor in EOC cells, leaving an intracellular fragment that can activate transcription and that can interact with TRKA, increasing its carcinogenic effects. Furthermore, NGF could modulate the immune response, since it can reduce CRT translocation from the endoplasmic reticulum to the cell membrane, reducing cancer cells' recognition by immune cells.

Additionally, it is relevant to point out that recent reports describe how NGF regulates the expression of different miRs, which in turn could affect the translation of protein participants of the abovementioned processes. Some examples include miR-143, whose levels are downregulated EOC and correlate with an increase of COX-2 levels. Another miR regulated by NGF is miR-222, which targets the metalloproteinase inhibitor TIMP3, an ADAM17 inhibitor. Furthermore, NGF stimulation reduces miR-23b levels through c-Myc, targeting the cell cycle and tumor growth proteins. Therefore, there is evidence to suggest that NGF-dependent miR regulation could lead to tumor development. Nevertheless, further studies are needed to confirm NGF's role in EOC; therefore, it is important to evaluate new miRs associated with EOC. These findings could result in new biomarkers used for diagnosis or target molecules that could allow the development of new therapies.

Abbreviations

ADAM17	a disintegrin and metalloproteinase domain-containing protein 17
COX	cyclooxygenase
CRT	calreticulin
EOC	epithelial ovarian cancer
ER	endoplasmic reticulum
FSH	follicle-stimulating hormone
FSHR	follicle-stimulating hormone receptor
LH	luteinizing hormone
LHR	luteinizing hormone receptor
miR	micro-RNA
NGF	nerve growth factor
Nts	nucleotides
p75NTR	p75 neurotrophin receptor
PGE2	prostaglandin E2
TRK	tyrosine receptor kinase
VEGF	vascular endothelial growth factor

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