Review Article

The Potential Role of Interleukin-11 in Epithelial Ovarian Cancer

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Abstract

Interleukin-11 (IL-11) has recently gained attention in cancer biology, and there is now an upsurge in IL-11 research with studies implicating a role of IL-11 in several human cancers of epithelial and hematopoietic origins. The identification of the pro-tumorigenic activities elicited by IL-11 has placed a new focus on generating therapeutic agents that will inhibit the IL-11 signaling pathway. However, the precise role of IL-11 signaling remains elusive in epithelial ovarian cancer (EOC). The purpose of this review is to describe the ovarian tumor microenvironment and delineate the possible sources and functions of IL-11 in EOC. Taking a holistic view of the dynamics of IL-11 in other cancer types, we have elucidated the potential role of IL-11 signaling in ovarian tumor cell biology and have also provided future recommendations to exactly decipher and target the signaling pathway in EOC. Improved understanding of the ovarian tumor microenvironment, particularly the IL-11 biology, would shed more light on EOC progression and enable the design of better-targeted therapies to manage this disease effectively.

Keywords: Interleukin-11; Epithelial ovarian cancer; Tumor microenvironment

1. Introduction

Ovarian cancer is known to be the seventh most common cancer in human females worldwide [1], and approximately 1,500 Australian women are diagnosed with the disease (mostly with an advanced stage) per annum. The five-year survival rate for ovarian cancer patients is only 43% [2]. About 9 out of 10 tumors of the ovary diagnosed (90%) are epithelial ovarian tumors [3].

Epithelial ovarian cancer (EOC) is the most frequent cause of gynecological cancer-related deaths [4]. Epithelial ovarian cancer (EOC) tumors have been largely categorized into two distinct groups with unique histological, clinical and molecular profiles. Type I ovarian cancers represent a minority of epithelial lesions and include low-grade and borderline serous cancers, endometrioid, mucinous and clear-cell cancers. The group has more frequent PTEN, PI3K catalytic subunit-α (PIK3CA), KRAS, BRAF and β-catenin (CTNNB1) mutations [5]. In general, these tumors are slow-growing, are confined to the ovary, and are less responsive to the conventional chemotherapy. In contrast, type II ovarian cancers represent a bulk of epithelial ovarian cancers and comprise high-grade serous cancers, mixed malignant mesodermal tumors, carcinosarcomas, and undifferentiated cancers. These tumors possess TP53 mutations in a vast majority of cases along with remarkable genomic instability and originate more commonly from the Fallopian tubes and the ovarian surface epithelium [5]. These tumors are clinically aggressive and are often widely metastatic at the time of diagnosis. Ovarian cancers in women with inherited BRCA1 and BRCA2 mutations are typically type II.

Ovarian cancer remains difficult to treat owing to the high recurrence rate. Platinum and taxane-based chemotherapy is the first line of treatment for all EOC patients after debulking surgery. Around 40-60% of patients attain a full clinical response to first-line chemotherapy. However, nearly 50% of these patients relapse within five years and only 10-15% of patients diagnosed with the advanced stage of the disease attain long-standing remission [6]. It is clear that clinical recurrence due to chemoresistance is inevitable in the vast majority of cases. Therefore, a detailed understanding of acquired and innate chemoresistance is required for better management of this lethal disease.

Chemotherapy for EOC patients typically involves combining a platinum-based drug such as carboplatin or cisplatin with a taxane such as paclitaxel (Taxol) or docetaxel. The mechanism of action of paclitaxel is generally linked to its suppression of microtubule dynamics. Cisplatin, on the other hand, crosslinks with the purine bases on the DNA and interferes with DNA repair mechanisms to cause DNA damage and apoptosis induction in cancer cells. Chemoresistance to paclitaxel and/or cisplatin is associated with the aberrant activation of signal transducer and activator of transcription 3 (STAT3) [7-9]. Early induction of pSTAT3 (Tyr705) post-cisplatin treatment has been correlated with cancer progression and subsequent relapse [10]. STAT3 is activated in chemoresistant ovarian tumors and in many other cancer types and can regulate pathways involving tumorigenesis, cell proliferation, angiogenesis and epithelial-mesenchymal transitions (EMT) [11]. Enhanced activation of STAT3 has been observed in ascites-derived recurrent ovarian tumors. The finding that the abrogation of cisplatin-induced STAT3 activation reduces tumorigenicity and cancer stem cell-like phenotype of EOC cells [8] emphasizes the role of STAT3 in chemoresistance. Further understanding of the exact cause of aberrant STAT3 activation in recurrent ovarian tumors is required to circumvent cisplatin and paclitaxel resistance and ultimately improve therapeutic outcomes for EOC patients.

Upstream growth factor and cytokine signaling through multiple transmembrane receptors can enhance the activation of STAT3 and promote tumor progression. Both IL-6 and IL-11 are known to signal via the JAK-STAT pathway and can activate STAT3 [12]. An upstream cytokine that activates STAT3 in EOC would be an ideal target.

Although the role of IL-6 is well understood in EOC progression, to date very little is known about the role of IL-11. Previously just one study, dated back to 2001, had reported on the IL-11/IL-11R axis. They observed that IL-11R expression was common in EOC, but the frequency of expression of IL-11 in ovarian tumors was very low [13]. The study didn't mention any clear source of IL-11 in the ovarian tumor microenvironment and also failed to find a precise role of IL-11/IL-11R signaling.

The purpose of the review is to address this problem in EOC biology and highlight the potential functions of IL-11 in EOC microenvironment. The main reason to why IL-11 is of particular interest and deserves attention in EOC is its prominent pro-tumorigenic nature in gastrointestinal cancer [14] and the emerging evidence implicating its role in several human cancers of epithelial and hematopoietic origins.

An appropriate understanding of the IL-11 biology would shed more light on the crosstalk between the EOC and its stroma and unravel its role in EOC progression. This advanced knowledge would establish whether or not the IL-11 signaling is associated with chemoresistance in EOC and would also enable the design of better-targeted therapies. The review compiles, discusses and consolidates our current perception of interleukin-11 and STAT3 biology in epithelial ovarian cancer and other cancer types. Finally, the review attempts to elucidate the possible sources and roles of IL-11 in EOC by mimicking its protumorigenic nature seen in other cancer types.

2. IL-11 in Human Physiology

IL-11 is a member of the IL-6 family of cytokines that comprises nine secreted soluble ligands: ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), cardiotrophin-like cytokine (CLC), IL-6, IL-11, IL-27, IL-31, leukaemia inhibitory factor (LIF) and oncostatin-M (OSM) [15]. Each ligand binds to a specific non-catalytic transmembrane receptor alpha chain. The family also uses the ubiquitously expressed transmembrane glycoprotein-130 (GP130, also known as IL6ST or CD130) beta-subunit [15]. IL-6 and IL-11 are the only family members to utilize GP130 as a homodimeric complex [16].

IL-11 was derived from bone marrow stromal cell line supernatants as a 19 kDa soluble factor that stimulated the proliferation of a plasmacytoma cell line that was otherwise IL-6 dependent [17]. The characteristic type 1 four-helix bundle conformation was revealed by the crystallization of the 178 amino acid human IL-11 protein. Its structure is somewhat distinct from its closest relative IL-6 [18]. The 7 kb human *IL-11* gene is localized to chromosome 19q13.3–19q13.4 and includes five coding exons [19]. The identifiable sources of IL-11 are B cells, cardiac myocytes, chondrocytes, fibroblasts, gastrointestinal epithelial cells, hepatocytes, macrophages, osteoblasts, synoviocytes, T cells and trophoblasts among others. However, the main source of IL-11 secretion is still unclear [20]. Although low levels of IL-11 mRNA are present throughout the body, it is hardly detected in the serum of healthy individuals. However, IL-11 levels are readily detectable in many inflammatory diseases and cancers [20].
IL-11 is a pleiotropic cytokine with demonstrated multiple actions: enhances platelet recovery following chemotherapy-induced thrombocytopenia, supports erythropoiesis, regulates macrophage proliferation and differentiation, modulates antigen-antibody responses and regulates bone cell proliferation and differentiation [16].

It also has functions in many other tissues, including the brain, gut, kidney, lung, and liver [16]. Although regarded as an anti-inflammatory cytokine with evidence supporting the efficacy of IL-11 in inflammatory diseases, few studies have demonstrated the pro-inflammatory function of IL-11. IL-11 may promote the inflammatory response observed in multiple sclerosis by stimulating the differentiation of naive $CD4^+$ T cells into Th17 cells [21]. IL-11 may participate in mast cell hyperplasia in various inflammatory skin conditions [22].

IL-11 has cyto-protective effects too. These actions are well reported in the gastrointestinal tract of rodents where IL-11 guards against various forms of mucosal injury. IL-11 shields small intestinal cells from collective radiation, chemotherapy, and ischemia in mice [23, 24]. The mechanism(s) of protective actions of IL-11 on mucosae are not entirely known. The reduction of injury may be due to both anti-inflammatory and direct cytoprotective effects of IL-11. IL-11 stimulates endothelial cells to diminish inflammation-associated injuries in both *in vitro* and *in vivo* models and, thus, plays a protective role in immune-mediated injuries [25]. This protective action of IL-11 has been attributed to its ability to activate the expression of antiapoptotic protein survivin through the STAT3 pathway in endothelial cells [25]. IL-11 may also play a key role in neurogenesis through direct stimulation of and acting as a differentiation factor for neuronal progenitor cells [26] (Table 1).

Pleiotropic Effects of IL-11		
Effect	**Observation**	**Reference**
Cytoprotective & Prosurvival	Mucosal (small intestinal) recovery	[102] [23] [24]
	Stem cell survival (small intestinal)	[103]
	Megakaryocytopoiesis	[24] [104]
	Erythropoiesis	[105]
	Neurogenesis	[26]
	Oligodendrocyte survival & maturation	[106]
	Osteoclast development	[107]
	Decidua & fetoplacental development	[27]
	Reduces hepatocyte necrosis & apoptosis	[108]
	Protects against renal ischemia and reperfusion injury	[109]
Anti-Inflammatory Effects	Inhibits macrophage TNF-α, IL-1β, IL-6 and IL-12 production	[110] [111] [112]
	Reduces Th1 cytokines	[111]
	Decreases IFN-γ	[111]
Pro-Inflammatory Effects	Induces differentiation of naive CD4+ T cells into Th17 cells (observed in multiple sclerosis)	[21] [22]
	Promotes mast cell growth	
Cell Migration	Stimulates human extravillous trophoblast migration	[28]

Table 1: Summarizes the important effector functions of IL-11.

IL-11 is also a key factor in human trophoblast function and placentation. Bilinski et al. [27] had earlier shown that maternal IL-11Rα signaling is essential for normal organization of the decidua and fetoplacental development. A recent study by Paiva et al. [28] has demonstrated that IL-11 induces human extravillous trophoblast (EVT) migration, but not proliferation, possibly via STAT-3 which indicates an important role for IL-11 in placentation. Elevated IL-11 levels result in physiological alterations at the maternal-fetal interface, leading to abnormal placentation and pregnancy complications including preeclampsia, intrauterine growth restriction (IUGR) and preterm birth [29].

3. Multiple Facets of IL-11 in Cancer Biology

Cytokines exert diverse biological effects and are an important component of innate immunity. As a result, cytokines engaged in cancer-related inflammation have been a subject matter of intensive research and therapeutic applications. Among cytokines that are associated with cancer-related inflammation, greater emphasis has traditionally been placed on IL-6 that links chronic inflammation and cancer development [30]. However, unlike IL-6, the role of IL-11 in various inflammation-associated cancers is newly emerging. Surprisingly, IL-11 has generally been deemed as an anti-inflammatory cytokine, in contrast with the pro-inflammatory IL-6, having direct effects on macrophages and other effector cells at the inflammation site [12].

IL-11 is a prominent tumor-promoting cytokine. Emerging evidence implicates a role of IL-11 in several human cancers of epithelial origin; including breast [31], gastric [14] and colon [32] cancers; and of hematopoietic origin [33]. Elevated IL-11 expression levels are linked to poor prognosis in human cancers. For example, in endometrial and gastric adenocarcinomas the expression of IL-11 escalates with tumor grade while in breast cancer the level of IL-11 can predict the development of metastatic spread to the bone [16, 34]. A new study has suggested an important role of IL-11 in NRF2-addicted tumorigenesis and that IL-11 is a promising therapeutic target for NRF2-driven breast cancers [35].

Appraisal of the recent literature strongly indicates a complex multi-faceted protumorigenic role for IL-11. IL-11 can increase the tumorigenic capacity of cells. Putoczki et al. [14] conclusively demonstrated that IL-11 signaling is essential for tumor onset and progression showing that mice lacking IL-11Rα developed very few tumors in colitis-associated cancer and sporadic colon cancer models. IL-11 signaling has been recognized to lead to the growth of osteosarcoma cells via the upregulation of IL-11Rα [36]. In addition, IL-11 signaling may enhance cell motility of chondrosarcoma cells, further suggesting its role in cancer progression [37]. Interestingly, in a study by Wu et al. decreased levels of IL-11 are linked to poorer prognosis in transitional cell carcinoma (TCC) of the bladder [38]. The authors theorized that the downregulation of IL-11 diminished the protective, anti-inflammatory actions of IL-11 and, as a result, may promote bladder TCC tumorigenesis and progression [38]. While most cancers are associated with an upregulation of IL-11, the bladder TCC is correlated with low expression of IL-11.

In a recent study, Pasqualini et al. [39] have reported the results of preclinical and early clinical evaluations of a novel therapy targeting IL-11 receptor α (IL-11Rα) in metastatic prostate cancer. Pasqualini and colleagues developed a ligand-directed agent—bone metastasis-targeting peptidomimetic-11 (BMTP-11)—containing the CGRRAGGSC peptide motif that has previously been found to bind to IL-11Rα in the tumor vascular endothelium, and a pro-apoptotic motif, $_{D}$(KLA-KLAK)$_{2}$, internalization of which induces apoptosis of the cell in preclinical models of cancer. Lewis et al. [40] too have evaluated the efficacy of IL-11Rα–targeted proapoptotic BMTP-11 in preclinical models of primary intratibial osteosarcomas and have observed a clear reduction of both tumor growth and lung metastases. Their findings corroborate the importance of developing IL-11Rα-targeted approaches and present BMTP-11 as a leading drug candidate for clinical translation for the benefit of high-risk osteosarcoma patients.

IL-11 has also been implicated in several other aspects of tumor biology. These include the stimulation of angiogenesis, survival under hypoxia, chemoresistance, as well as expansion and survival of early micrometastatic colonies in bone and soft tissues including liver and lung [31]. The latest study emphasizing the function of IL-11 in cancer development is that of Pastor et al. [41], who established that IL-11 in bronchoalveolar lavage fluid (BALF) is a highly specific diagnostic biomarker for lung adenocarcinoma (Table 2).

4. IL-11 and Epithelial Ovarian Cancer

Normal ovarian tissue is rich in cytokines and chemokines, which are essential in the ovarian physiology and ovulation. They regulate the growth, differentiation, and apoptosis of various cellular components of the ovary. Campbell et al. [13] investigated IL-11 and the IL-11 receptor subunits' expression in primary human benign and malignant tumors as well as in normal ovaries. They found that the malignant epithelial cells in the majority of the primary ovarian carcinoma samples expressed IL-11Rα. Co-expression of IL-11Rα and GP130 was also found in most primary ovarian carcinoma samples (Table 2). Moreover, benign ovarian tumors, normal ovarian epithelium, and ovarian stromal cells also expressed IL-11Rα and GP130 (Table 3). However, IL-11 mRNA was expressed in only 14.3% malignant samples studied. Although it was demonstrated that IL-11Rα and GP130 subunits were commonly expressed within ovarian epithelial cells of both malignant and nonmalignant primary tissues, the exact role of the IL-11 receptor system in ovarian epithelial cell biology was not established [13].

Gynaecological and Other Cancers Associated with IL-11 Signaling		
Cancers Associated with Enhanced IL-11 Signaling		
Cancer	**Observation**	**Reference**
Endometrial	Positively associated with higher tumor grades Contribute to migration and metastasis of high-grade cancer	[48] [115] [49] [51]
Ovarian	Presence of IL-11Rα	[13]
Bone	Cell lines and primary tumors express IL-11 Promotes cell motility	[116] [36] [40] [37]

Breast	Required for primary tumor growth and metastasis	[117] [31] [34]
Colorectal	Required for primary tumor growth and Metastasis	[88] [14]
Glioblastoma	Cell lines express IL-11	[118]
Hodgkin's lymphoma	Presence of IL-11Rα	[119]
Liver	Associated with bone metastasis	[120] [121]
Leukemia	Elevated IL-11 and IL-11Rα	[33]
Lung	Elevated IL-11 IL-11 as a highly specific diagnostic biomarker Associated with chemoresistance	[122] [41] [89]
Pancreatic	Elevated in primary and advanced tumors	[123] [124]
Prostate	Associated with progression	[101] [125]
Renal	Cell lines express IL-11	[126]
Skin	Cell lines express IL-11	[127]
Stomach	Required for primary tumor growth and Metastasis	[128] [14]
Thyroid	Positively correlated with distant metastasis	[74]
Cancers Associated with Decreased IL-11 Signaling		
Cancer	**Observation**	**Reference**
Bladder transitional cell carcinoma (TCC)	Reduced levels of IL-11 correlated with poorer prognosis	[38]

Table 2: Shows at a glance all cancer types that are associated with IL-11 signaling.

A key question is what role the IL-11/IL-11 receptor axis might play in epithelial ovarian cancer biology. Perhaps the answer lies in the ovarian physiology. There is strong evidence that IL-11 is present in periovulatory follicular fluid (FF). Branisteanu et al. [42] demonstrated that IL-11 is present in FF and in conditioned medium from cultured granulosa cells, with higher concentrations in atretic follicles. The report raised the question of IL-11 involvement in the process of atresia.

The role IL-11 plays in folliculogenesis and/or oocyte development was not clear until Jang et al. [43] examined the regulation of IL-11 expression as well as the role of IL-11 during ovulation. They observed that LH stimulated the expression of IL-11 protein in theca cells and LH-stimulated IL-11 mRNA levels were repressed by protein kinase A and mitogen-activated protein kinase inhibitors (Table 4). Moreover, the treatment of preovulatory follicles with IL-11 stimulated progesterone production. This is by far the only study that has revealed for the first time the regulation and the role of IL-11 expression during ovulation. IL-11 in theca cells is activated by mitogen-activated protein kinase signaling and TLR4 activation, leading to enhanced progesterone production during ovulation [43] (Table 3). Interestingly, progesterone protects the ovary from neoplastic transformation [44]. Nonetheless, an intriguing question of what role IL-11R might play in ovarian epithelial cell biology is valid and is still unanswered given that it is commonly expressed within ovarian epithelial cells.

Mice made deficient in IL-11Rα via gene targeting appear to have functional ovaries although these mice are infertile, due to a defect in the ability of the uterus to undergo decidualization, resulting in failure of implantation [45]. Winship et al. [46] studied the autocrine and paracrine effect of IL-11 on human decidual and trophoblast cells during placental development. Insufficient IL-11 levels may disrupt the balance of decidual restraint and trophoblast invasion necessary for normal placentation, whereas elevated levels may obstruct trophoblast invasion necessary for a healthy pregnancy.

The expression of IL-11 has been observed in both human endometrial epithelial and stromal cells [47] (Table 3) (Table 4). IL-11 levels are elevated in uterine lavage fluid from endometrial cancer patients, and enhanced levels are positively correlated with higher tumor grades [48]. Moreover, elevated IL-11 levels may promote migration and metastasis of high-grade endometrial cancer cells via the STAT3 pathway [49] (Table 2). Targeting IL-11 receptor-alpha attenuates proliferation and invasion of human endometrial cancer cell *in vitro* and reduces tumor growth and metastasis *in vivo* [50, 51].

Gynaecological Tissues and Organs That Respond to IL-11 Signaling			
Tissue/Organ	**Cell Type**	**Response**	**Reference**
Endometrium	Epithelial cells	Increase TNF-α	[114]
	Endothelial cells	N/A	[48]
	Smooth muscle	N/A	[48]
Ovary	Epithelial cells	N/A	[13]
	Stromal cells	N/A	[13]
	Granulosa cells	Increase progesterone production & StAR gene expression	[43]
		Increase progesterone production & StAR gene expression	
	Theca cells		[43]

Table 3: Gynaecological Tissues and Organs That Respond to IL-11 Signaling.

Gynaecological Tissues and Organs That Produce IL-11			
Tissue/Organ	**Cell Type**	**Stimulators**	**Reference**
Endometrium	Epithelial cells Stromal cells	Endogenous	[113]
Ovary	Theca cells	Luteinizing hormone (LH)	[43]

Table 4: Gynaecological Tissues and Organs That Produce IL-11.

Having known a clear source of IL-11 production in the ovarian milieu from Jang et al. [43] study, what now has to be determined is whether IL-11R of the ovarian epithelium responds to IL-11 from theca cells or to IL-11 derived from an extra-ovarian source, and what role IL-11R might play in ovarian epithelial cell biology. Perhaps the answer might come from the report that suggests the potential involvement of IL-11 in the normal growth controls in the intestinal epithelium [52].

Whatever the role of IL-11/IL-11R axis in epithelial ovarian cell biology might be, however, the importance of IL-11Rα to epithelial ovarian cancer cannot be underestimated given its high frequency of expression [13]. It is possible that the dysregulation of the IL-11 signaling in the ovarian epithelium might be one of the factors in epithelial ovarian tumorigenesis. It is reasonable to assume that these tumor cells are able to disturb the homeostasis of cytokine expression including IL-11 in the ovary in such a way that the ovarian cytokine expression favors the growth of the tumor. Therefore, IL-11 deserves attention in EOC, and additional investigations are warranted to determine the precise role(s) of the IL-11 receptor system and associated autocrine/paracrine interactions in epithelial ovarian cancer biology.

5. IL-11 Signaling

IL-11 initiates signaling upon binding to the cognate IL-11Rα. The IL-11/IL-11Rα complex then interacts with the transmembrane glycoprotein β-receptor subunit GP130 leading to the formation of a hexameric complex in a 2:2:2 pattern (IL-11/IL-11Rα/GP130) [16]. The resulting receptor complex is called the interleukin-11 receptor, a type 1 cytokine receptor with GP130 receptor as a signal-transducing subunit. Since the expression of GP130 is ubiquitous, with the exception of pre-B-cells, the ability of cells to respond to IL-11 is governed by the expression of α-receptor subunits.

The hexameric complex facilitates juxta-positioning of the Janus (JAK) family tyrosine kinases JAK1, JAK2, and TYK2, which are constitutively coupled with a proline-rich intracellular domain of GP130, to permit trans-phosphorylation and kinase activation [53]. Activated JAK kinases, in turn, phosphorylate the various cytoplasmic tyrosine residues in GP130 to provide docking sites for the SH2 domain-containing signaling molecules [53]. Specifically, the four membrane distal pY residues in GP130 act as docking sites for the latent STAT1 and STAT3 (signal transducer and activator of transcription 1/3) transcription factors [16]. This allows JAK-mediated phosphorylation of a conserved Y residue in the carboxyl-terminal portion of these STAT proteins. The resultant STAT homo- or heterodimers, upon active translocation into the nucleus, bind to DNA in a sequence-specific manner to regulate gene transcription (Figure 1) [16].

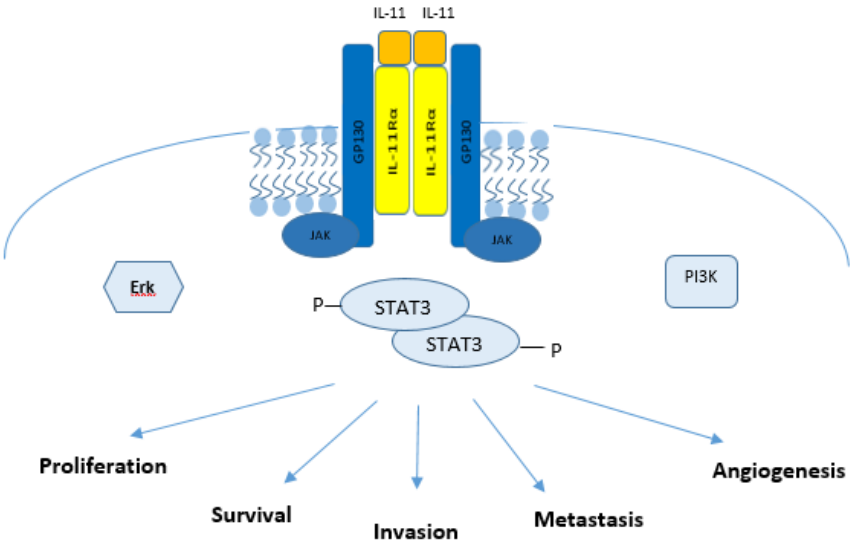

Figure 1: The IL-11/gp130/STAT3 signaling Axis: Formation of an IL-11 signaling complex leads to the recruitment of JAKs which permit the phosphorylation of STAT3. Activated STAT3 when bound to DNA results in increased pro-cancerous gene transcription.

Among the transcriptional target genes for STAT3, SOCS3 (suppressor of cytokine signaling 3) is an important negative regulator of GP130 signaling. Through its SH2-domain, SOCS3 binds to GP130 and interacts simultaneously with a JAK molecule to occlude access to the substrate binding pocket of JAKs. GP130 also serves as a docking site for the Y-phosphatase SHP2/PTPN11, which provides the framework for GP130-dependent activation of the RAS/ERK signaling cascade [16]. Finally, GP130 is able to activate the phosphatidylinositol 3' kinase (PI3K)–AKT–mTORC1 pathway that does not require tyrosine phosphorylation of GP130 [54]. Genetic evidence suggests that STAT3 activation is the most important event to transduce a majority of GP130-family cytokines' signals [55].

6. STAT3 Signaling

IL-11 can confer most of the 'hallmark' capabilities to neoplastic cells, provided they express the cognate IL-11Rα receptor subunit, through the STAT3 signaling pathway. STAT3 is associated with a majority of the six crucial alterations in cellular physiology (i.e. self-sufficiency in growth signals, insensitivity to growth-inhibiting signals, resistance to apoptosis, unrestricted cellular replication, sustained angiogenesis and tissue invasion and metastasis) identified by Hanahan and Weinberg [56].

Indeed, aberrant STAT3 activation is a common characteristic in many human cancers of epithelial origin (i.e., breast, head and neck, stomach, colon) as well as hemopoietic origin (i.e., leukemias, multiple myeloma) [57]. Abundant evidence highlights that STAT3 is an ideal target for cancer treatment. Wen et al. [58] demonstrated that

knockdown of JAK1/STAT3 by using shRNA or a small-molecule inhibitor effectively restrained ovarian tumor progression. The results were consistent with the findings by Gritsina et al. [59], who showed the interruption of functions necessary for ovarian tumor growth and progression following the pharmacologic inhibition of the JAK2/STAT3 pathway. RNAi-mediated knockdown of STAT3 repressed the growth of human ovarian cancer through the downregulation of cyclin D1, c-Myc and Bcl-2 [60].

In addition to its known roles in promoting tumor cell proliferation, survival, invasion, angiogenesis and immunosuppression, STAT3 oncogenic pathway has recently been shown to confer drug-resistance, radio-resistance, and cancer stem cell-like phenotype. Autocrine interleukin-6 production has been shown to confer cisplatin and paclitaxel resistance in ovarian cancer [82]. However, no study has yet reported the presence of IL-11 in the ascites. It is surprising that even though IL-11Rα is commonly expressed by ovarian tumor cells, the IL-11 function is not well-characterized in ovarian cancer biology [13]. Nonetheless, the role of IL-11 in ovarian malignancy cannot be discounted. Castells et al. [83] proposed that mesenchymal stem cells (MSCs) activated the release of IL-6 and IL-8 by macrophages that mediate the acquisition of chemoresistance in human ovarian cancers. Yu et al. [84] studied the cell stemness capacity of a set of interleukins and identified that IL-3, IL-6, and IL-11 stimulated while IL-10 and IL-24 repressed the growth, invasion and migration of human prostate cancer cell lines. Furthermore, IL-3, IL-6 or IL-11 treatment reduced the chemosensitivity to docetaxel while IL-10 or IL-24 treatment enhanced the sensitivity to docetaxel. Therefore, IL-11 deserves attention in the EOC setting as well.
Recently, an unexpected function of IL-11 in colitis-associated cancer (CAC) has been reported [88]. Secreted TGF-β from the cancer cells stimulates IL-11 secretion (from cancer-associated fibroblasts) that activates STAT3 signaling via GP130 in tumor cells. This circuit increases the survival rate of metastatic cells, thereby increasing metastasis [88]. The crosstalk between cancer-associated fibroblasts (CAFs) and cancer cells through IL-11 is also seen in lung adenocarcinoma. The upregulation of IL-11 in CAFs post-chemotherapy supports lung adenocarcinoma cell chemoresistance through the activation of the anti-apoptotic IL-11R/STAT3 signaling pathway [89].

The role of IL-11 in cancer cell migration and invasion under the hypoxic environment has also been reported. Lim [100] demonstrated that the hypoxia-induced migration and invasion was attenuated following the inhibition of the IL-11-STAT3 axis in MDA-MB-231 breast cancer cells. Onnis et al. [101] had previously found that IL-11 was a hypoxia-inducible, VHL-regulated gene in human cancer cells and the transcriptional activation of the IL-11 promoter was mediated by the cooperative association between HIF-1 and AP-1. Silencing of IL-11 dramatically abrogated hypoxia-induced anchorage-independent growth and significantly diminished tumor growth in xenograft models [101]. Hence, an appropriate understanding of molecular cues that facilitate the crosstalk between the tumor and its stroma is necessary to design novel targeted therapeutics disrupting the prostemness tumor-stroma interaction.

7. Conclusions

The ovarian tumor microenvironment (TME) is now perceived as the pivotal factor in multiple phases of disease progression, particularly local resistance, immune evasion, and distant metastasis. Comprehensive understanding of

the TME will permit the evaluation and selection of novel drug candidates to target malignancies at both primary and metastatic sites.

Cytokines and chemokines play an important role in the physiology of the ovaries, for example in the regulation of ovulation. It is interesting to note that most of the cytokines that are expressed in normal ovarian tissue are also expressed in the microenvironment of ovarian cancer and are associated with malignancy. Traditionally much emphasis has been put on IL-6. The role of IL-6 in conferring cisplatin and paclitaxel resistance in ovarian cancer cells is well-characterized [82]. However, the role of IL-11/IL-11R axis remains elusive in epithelial ovarian cancer milieu although the IL-11R expression has been reported in EOC [13].

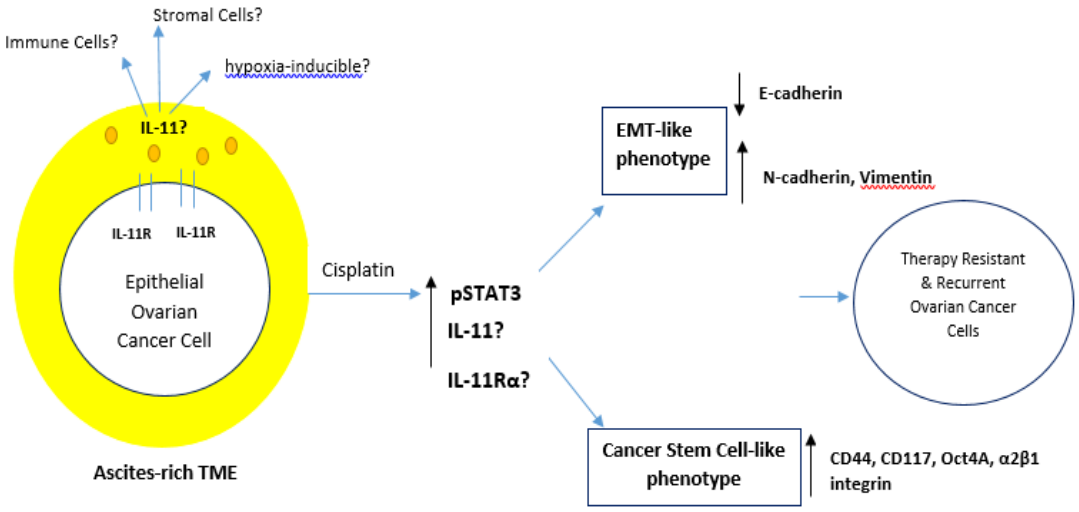

Figure 2: Potential Working Model of the Biology of Il-11 in EOC. The ascites-rich TME constitutes a complex reservoir of cellular components (CAFs, endothelial cells, MSCs and immune cells) and extracellular solutes (growth factors, cytokines and chemokines). Chemotherapy or hypoxia-induced IL-11 signaling in EOC may be correlated with EMT-like and/or Cancer stem cell-like phenotypes through the activation of STAT3.

There has been an upsurge in IL-11 research recently demonstrating that autocrine and paracrine IL-11 signaling is pro-tumorigenic in other cancer types. Roles of IL-11 in cyto-protection and cell migration in both physiological and pathological situations are now known. It is worth noting that cancer cells utilize these cytokines to their advantage by manipulating the TME. Understanding the biology of IL-11 in EOC is therefore imperative given the advancements in IL-11 research that reflect its biology similar to the more prominently studied IL-6. We have demonstrated a potential working model of its biology in Figure 2. Further investigations into the critical role of IL-11 signaling will also assist in the design of rational treatment strategies for women with EOC.

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