Biochimica et Biophysica Acta 1845 (2014) 117–125

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbacan

Review

Role of the interleukin 6 receptor family in epithelial ovarian cancer and its clinical implications

Janani Kumar, Alister C. Ward *

School of Medicine, Deakin University, Geelong, Victoria, Australia
Strategic Research Centre in Molecular and Medical Research, Deakin University, Geelong, Victoria, Australia

ARTICLE INFO

Article history:
Received 7 June 2013
Received in revised form 8 December 2013
Accepted 24 December 2013
Available online 2 January 2014

Keywords:
Epithelial
Ovarian cancer
IL-6R
Cytokine signaling
JAK–STAT pathway

ABSTRACT

Ovarian cancer is the most lethal gynecological malignancy, with few effective treatment options in most cases. Therefore, understanding the biology of ovarian cancer remains an important area of research in order to improve clinical outcomes. Cytokine receptor signaling through the Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathway is an essential component of normal development and homeostasis. However, numerous studies have implicated perturbation of this pathway in a range of cancers. In particular, members of the IL-6R family acting via the downstream STAT3 transcription factor play an important role in a number of solid tumors – including ovarian cancer – by altering the expression of target genes that impact on key phenotypes. This has led to the development of specific inhibitors of this pathway which are being used in combination with standard chemotherapeutic agents. This review focuses on the role of IL-6R family members in the etiology of epithelial ovarian cancer, and the application of therapies specifically targeting IL-6R signaling in this disease setting.

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Abbreviations: ECM, extracellular matrix; EGF, epidermal growth factor; EOC, epithelial ovarian cancer; G-CSF, granulocyte colony-stimulating factor; GP130, glycoprotein 130; IL, interleukin; JAK, Janus kinase; LIF, leukemia inhibitory factor; MAPK, mitogen-activated protein kinase; OBR, obesity receptor; OSM, oncostatin M; PI 3-K, phosphatidyl inositol 3-kinase; R, receptor; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription

* Corresponding author at: School of Medicine, Deakin University, Pigdons Road, Geelong, Victoria 3216, Australia. Tel.: +61 3 5227 2041; fax: +61 3 5227 2945.
E-mail address: award@deakin.edu.au (A.C. Ward).

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http://dx.doi.org/10.1016/j.bbcan.2013.12.003

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1. Introduction

Ovarian cancer is the most lethal gynecological cancer, with approximately 200,000 new cases diagnosed each year globally, and a greater than 60% mortality rate within five years [1]. This poor prognosis is partly due to the largely asymptomatic nature of the disease, such that the primary tumor has often already spread at the time of diagnosis [2]. However, there is also a limited understanding of disease etiology at the molecular level, which continues to hamper targeted therapeutic development.

2. Biology of ovarian cancer

2.1. Types of ovarian cancer

Ovarian cancer is not a single disease, but rather a spectrum of malignancies exhibiting distinct biology and histopathology. Ovarian cancers are grouped into three major categories based on the cells from which they originate [3,4]. Germ cell tumors are derived from oocytes, and represent approximately 10%–15% of all ovarian cancers [5]. Stromal (or 'Sex cord') tumors are formed from cells of the stromal mesenchyme/sex-cord within the ovary, and may contain gonad-related cells, as well as immature fibroblasts and connective tissue-forming cells [6]. These represent about 5% of all ovarian cancers with tumors arising from granulosa cells being the most prevalent type [5]. However, the most common form of this disease is epithelial ovarian cancer (EOC), representing about 80% of all cases. EOC consists of distinct histological subtypes: predominantly serous (cells resembling the internal lining of the fallopian tube), endometrioid (cells resembling endometrium), clear cell (hobnailed shaped cells with clear cytoplasm) and mucinous (cells resembling endocervical epithelium) [7–9]. Serous is the most common subtype, representing around 70% of EOC [10]. Each EOC subtype is further divided into benign, borderline and malignant, based on the level of containment, and graded from I to IV, depending on the extent of differentiation [3], with some specific genetic alterations identified [11,12]. EOC, especially the predominant serous subtype, is mainly thought of as originating from the malignant transformation of the ovarian surface epithelium (OSE) [13] (Fig. 1). However, some researchers have argued that the key site is the fallopian tube, which shares a common embryonic origin to the OSE [14,15].

2.2. Epithelial ovarian cancer progression

During the transformation process, EOC cells acquire additional properties, such as increased cell proliferation, survival and migration. There are specific changes in cell–cell and cell–extracellular matrix (ECM) interactions, with increased proteolysis and ECM degradation observed. This culminates in the shedding of tumor cells into the peritoneum, where they survive in an anchorage-independent manner as cellular aggregates or spheroids, until they attach to a suitable secondary site for further growth [16,17] (Fig. 1). There is also a growing consensus that EOC, like many other cancers, is a stem cell disease in which a small population of cells has acquired the ability to both self-renew as well as generate the cell types that are characteristic of the tumor [18].

Women with EOC typically present with advanced-stage disease, when the cancer has already spread throughout the peritoneum, and in some cases, to distant metastatic sites. With aggressive surgery supplemented with paclitaxel and platinum-based chemotherapy, most patients initially return to a state of microscopic disease with minimal residual tumor. However, this is usually short-lived, with recurrent disease characterized by increased metastatic behavior, as well as acquisition of drug-resistance to multiple types of chemotherapy via increased activity of the ATP-binding cassette (ABC) drug transporters, enhanced DNA repair and reduced apoptosis [19]. Only ~30% of patients with recurrent disease survive for >5 years [4].

2.3. Immune responses to epithelial ovarian cancer

The clinical outcome of EOC is strongly dependent on the immune response [20], which is critically dependent on macrophages, the most prevalent immune cell within the EOC microenvironment. 'M1' macrophages elicit strong anti-tumor immunity, whereas 'M2' macrophages suppress adaptive immunity, and promote tumor survival, invasion and metastasis [21]. Tumor-associated macrophages (TAMs) are mostly identified as being of the M2 type, with their density correlating with poor prognosis in EOC [22]. With regard to other immune cells, higher numbers of infiltrating T cells are associated with increased survival [23], with a better prognosis with a Th1 response compared to a Th2 response [24]. Increased levels of Th17 cells have also been observed in ovarian cancer [25], but these may in fact enhance tumorigenesis [26]. Tolerogenic dendritic cells are able to suppress T cell effector functions to promote cancer development [27,28].

2.4. Cytokines in epithelial ovarian cancer

Cytokines are small polypeptides released from cells to regulate the activities of other cells via interactions with specific cytokine receptors expressed on their surface [29]. They are able to stimulate proliferation, differentiation, survival and activation [7]. At least 16 different cytokines are expressed in normal ovaries, along with many of the corresponding

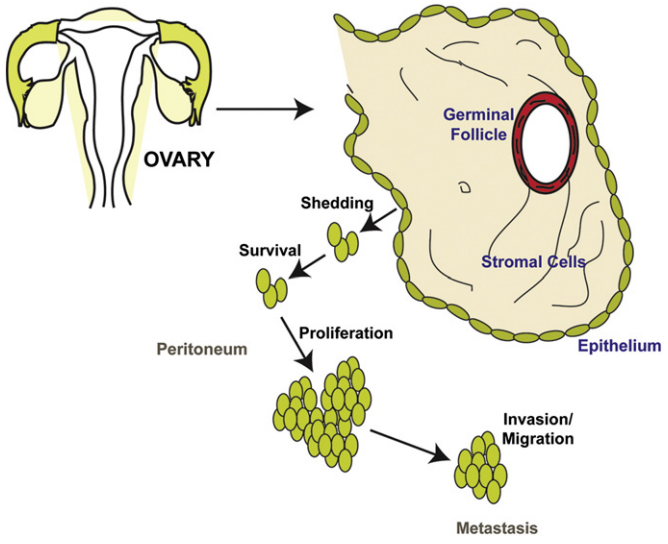

Fig. 1. Biology of ovarian cancer and its progression. Diagrammatic representation of the cell origins of ovarian cancers: germinal, stromal and epithelial. The progression of epithelial ovarian cancer is demonstrated in more detail, including the role of some key cancer phenotypes, which include proliferation, survival, invasion/migration, angiogenesis and chemoresistance.

receptors [30]. In ovarian cancer there is increased expression of particular cytokines and/or receptors [31]. These act – along with growth factors such as EGF – to enhance key phenotypes associated with tumor progression, such as proliferation, migration and survival, including chemoresistance [17]. This can be due to direct effects on the cancer cells themselves, or via indirect effects on components of the immune system.

3. The IL-6R family

3.1. Structure and function

Cytokines that act via members of the so-called interleukin-6 receptor or "IL-6R" family of cytokine receptors (Fig. 2) are of particular relevance to EOC. The core members of this family employ a ligand-specific receptor α chain in combination with a shared receptor chain, glycoprotein 130 (GP-130), and sometimes a third receptor chain. However, also in this family are receptors that utilize GP130-related receptor chains, including granulocyte colony-stimulating factor receptor (G-CSFR) and obesity gene receptor (OBR), which form homomeric complexes [32]. Soluble forms of several receptors exist, including of the IL-6R (sIL-6R), which can bind ligand extracellularly before associating with signaling chains on target cells [33].

Individual IL-6R family members have distinct functions: for example, IL-6R mediates immune, hematopoietic and hepatic responses, and contributes to follicle development in normal ovaries [34,35], leukemia inhibitory factor receptor (LIFR) functions in stem cell maintenance, neural and hematopoietic development [36], oncostatin M receptor (OSMR) has a role in the differentiation and survival of neural and hematopoietic cells [37], G-CSFR promotes granulocytic development, hematopoietic stem cell mobilization and myeloid cell migration [38], while OBR, the receptor for leptin, functions in the regulation of energy intake and energy homeostasis [39]. The expression of these receptors and their cytokine ligands is normally tightly controlled. Overexpression of both IL-6 and its receptors (IL-6R and sIL-6R) in the serum of cancer patients has typically been associated with poor clinical outcomes [40].

3.2. Downstream signaling

Within the IL-6R family, the common utilization of GP130 or related receptor chains to transduce intracellular signals means that similar downstream pathways are activated [32]. These include the mitogen-activated protein kinase (MAPK), phosphatidyl-inositol 3-kinase (PI3K) and, probably most importantly, the Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathways [33,41]. JAK tyrosine kinases are constitutively associated with IL-6R family members and are activated following ligand binding [33]. These phosphorylate receptor tyrosines, forming docking sites for signaling molecules including STATs, which in turn also become activated. While other JAKs and STATs may also be involved, virtually all members of the IL-6R family utilize the JAK1/2–STAT3 signaling pathway as a core mechanism for mediating their downstream effects [42]. Phosphorylation of STAT3 causes it to dimerize and translocate from the cytoplasm to the nucleus where it initiates changes in the transcription of a number of genes, including those affecting growth, differentiation, and survival [43,44]. Although the full spectrum of STAT3 target genes is yet to be defined, several have been identified that contribute to specific phenotypes (Fig. 3) [45]. These include the pro-proliferative genes Cyclin D1 and c-MYC [46], the anti-apoptotic genes BCL-2, Survivin and MCL-1 [46], genes involved in migration/invasion, such as MMP-9, CXCR4, CXCL12 and Integrins [47,48], the pro-angiogenic genes VEGF and Notch3 [46], as well as genes mediating chemoresistance, including MDR1 and GSTpi [49]. In addition, genes encoding feedback regulators, such as suppressor of cytokine signaling (SOCS) 3 [50] are also induced, acting in combination with tyrosine phosphatases and other regulatory proteins to extinguish signaling from IL-6R family members [51].

4. Role of the IL-6R family in epithelial ovarian cancer

There is increasing evidence that signaling via specific IL-6R family members may play a significant role in the progression of various cancers, including EOC.

4.1. IL-6R

IL-6 is a potent, pleiotropic cytokine that acts via a receptor complex consisting of the ligand-binding IL-6Rα chain and the signal-transducing GP130 chain, both of which are widely expressed [33].

IL-6 has been implicated in a wide range of cancers, such as multiple myeloma [52], endometrial cancer [53], lung cancer [54], colorectal cancer [55], renal cell carcinoma [56], cervical cancer [57] and breast cancer [58]. IL-6 is known to directly promote tumor cell attachment, proliferation and migration through the activation of several downstream signaling pathways, including both the JAK–STAT and MAPK cascades [40]. Other studies have shown that IL-6 can also enhance survival [58] and angiogenesis [59]. Unchecked production of IL-6 can also lead to chronic inflammation, which is implicated in many types of cancer [60].

IL-6/IL-6R signaling is important in EOC. IL-6 is constitutively secreted from the ovarian cancer microenvironment, either directly from ovarian cancer cells or through secondary inflammation [61,62]. IL-6 production is increased by EGF stimulation in advanced-stage epithelial ovarian cancer [63] and relevant cell lines [64], indicating cross-talk between growth factors and cytokine signaling. High plasma levels of IL-6 correlate with poor prognosis [65–68], and are associated with ovarian cancer subtypes with poorer outcomes [69]. Increased expression of the IL-6R has also been observed in EOC [48,64,70]. This includes soluble forms of the receptor, generated either via alternate splicing or increased expression of sheddases that cleave the full-length receptor, which can mediate effects in tumor cells as well as adjacent stromal cells or peritoneal cells [70].

IL-6/IL-6R signaling can act in a number of ways to augment ovarian cancer progression. IL-6 can act directly on ovarian cancer cells to enhance migration, attachment and invasion [48,64,71], and facilitate

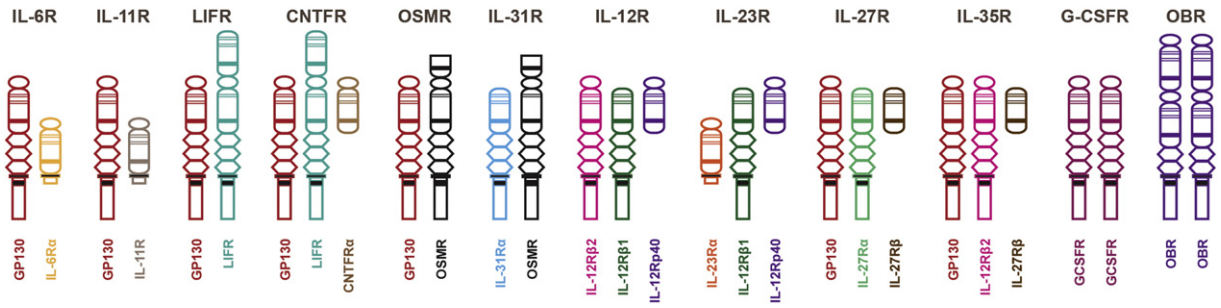

Fig. 2. The interleukin-6 receptor family. Schematic representation of the IL-6R family members, showing their constituent receptor chains, which are indicated below.

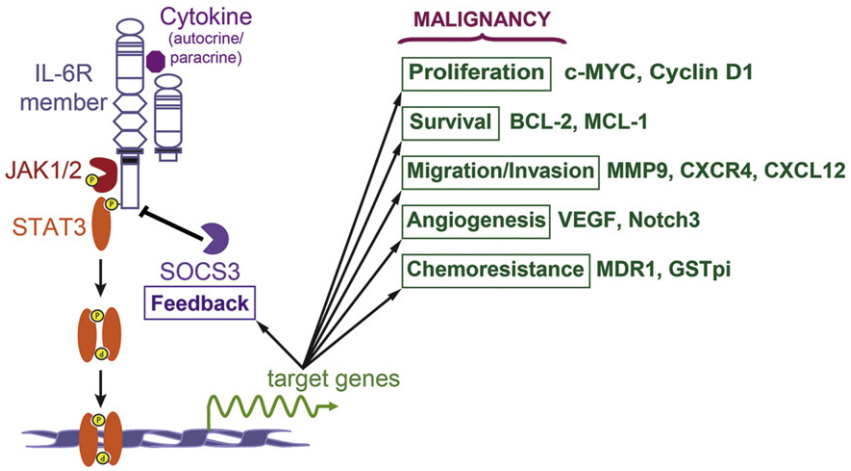

Fig. 3. IL-6R family signaling in ovarian cancer. Signaling from the IL-6R family of receptors (autocrine or paracrine) via JAK1/2–STAT3 and its impact on expression of target genes involved in the key malignant phenotypes of proliferation, survival, migration/invasion, angiogenesis and chemoresistance, as well as negative feedback.

anchorage-independent growth [48]. For example, an IL-6R-positive EOC cell line exhibited ~50% increased tumor formation in mice compared with cells lacking IL-6R expression [70]. Finally, IL-6 can enhance chemoresistance [49,72], through increased expression of multi drug resistance pumps and anti-apoptotic genes in ovarian cancer cells [49]. Consistent with this, IL-6 is observed in the serum and ascites of patients harboring resistant cancers [66,67,73,74].

IL-6 can also act indirectly, via a number of mechanisms [59,75]. Firstly, it can polarize macrophages toward the M2 phenotype [76–78]. These TAMs are able to suppress immune responses as well as stimulate angiogenesis through VEGF and IL-8 production, and promote metastasis via MMP-2 and MMP-9 [48,79]. Secondly, IL-6 can preferentially differentiate $CD4^+$ T cells toward Th17 subsets [80], which can be further expanded by this cytokine within the ovarian tumor microenvironment [25]. These Th17 cells can promote tumor growth by increasing the density of the microvasculature in EOC [81], as well as inducing further IL-6 production [82]. Thirdly, IL-6 can mediate the induction of tolerogenic dendritic cells [83]. Fourthly, IL-6 can also stimulate expression of the inhibitory co-stimulatory molecule B7-H4 on both tumor and immune cells, further suppressing immunity [84]. Finally, IL-6 has been shown to blunt the potency of chemotherapeutic agents through its actions on endothelial cells [85].

4.2. IL-11R

The receptor complex for IL-11 consists of IL-11Rα and GP130 [86]. IL-11R signaling supports the growth of multiple hematopoietic progenitors as well as exerting metabolic and cytoprotective effects on cells outside the hematopoietic system [87].

IL-11 has been shown to regulate adhesion and migration of chondrosarcoma [88] and endometrial cancer [89], and was recently demonstrated to be the dominant cytokine in the etiology of gastrointestinal cancer [90]. IL-11R is expressed on >90% of EOC, with expression of its ligand much less common [91]. However, the function of IL-11/IL-11R in EOC remains uncertain. This is of particular clinical relevance, since IL-11 is being developed as a treatment for chemotherapy-induced thrombocytopenia [92].

4.3. LIFR

The LIFR consists of a heterodimer of the LIFRα chain and GP130, which acts as a receptor for leukemia inhibitory factor (LIF), cardiotrophin-1 (CTF1), as well as oncostatin M (OSM) [36]. LIFR is expressed on a wide range of hematopoietic cells and cell lines originating from bone marrow, thymus, spleen, liver, placental tissue, and peritoneum [93], with LIFR signaling shown to be important for the maintenance of embryonic stem cells, embryo implantation, neuronal survival and hematopoiesis via LIF [36], and in cardio protection via CTF-1 [94].

The functional significance of LIFR in human solid tumor cell lines is not fully understood, but LIF and LIFR has been found to be expressed in breast, kidney and prostate cancer cell lines, and can induce tumor growth in these cells in either an autocrine or paracrine manner [95,96]. Ovarian carcinomas consistently express LIFR [97], with altered expression of LIFR linked to chemoresistance [98]. Elevated LIF has also been associated with EOC [27,99], where it appears to correlate with the clinical characteristics of the tumor [99]. LIF may also act indirectly by contributing to the development of immune deficiency within the peritoneal cavity [27], as well as augmenting to the development of TAM-like cells [100].

4.4. OSMR

The mammalian OSMR complex comprises OSMRα and GP130 [101], and is expressed on many cell types, including endothelial cells, hepatic cells, lung cells and bone marrow cells [102]. OSMR signaling is able to influence the development of blood cells, liver, and specific neuronal populations [37].

OSMR has been shown to be frequently expressed in tumors, where it can activate downstream signaling pathways upon ligand stimulation [97]. OSM has been demonstrated to suppress the growth of a subset of breast and lung carcinoma cell lines [103,104], but to increase proliferation of prostate carcinoma cell lines [105]. Ovarian carcinomas consistently express OSMR and OSM [97,106], although their role in this setting is also controversial. One group has suggested that OSM can strongly stimulate proliferation [106], while another has suggested that OSM exerts a small effect on survival, but not growth [97].

4.5. IL-12R

The IL-12R consists of a heterodimer of IL-12Rβ1 and IL-12Rβ2, which is activated by a heterodimer of the cytokine IL-12p35 and the soluble cytokine receptor IL-12p40 [107]. IL-12 is a pro-inflammatory cytokine, with IL-12R signaling playing a central role in promoting tumor immune-surveillance, which has seen it used in various modalities to activate the immune system in cancer [108].

IL-12 has been shown to be overexpressed in EOC, with expression significantly associated with both increased overall survival [109] and

reduced disease progression [110]. This has led to IL-12 being used in the context of EOC, with a plasmid-based IL-12 therapy is in clinical trials for platinum-sensitive ovarian cancer [111]. IL-12 transduced MSCs have also been shown to inhibit ovarian carcinoma cells both in vitro and in vivo [112].

4.6. IL-23R

The IL-23R consists of the ligand-specific IL-23Rα and the shared IL-12Rβ1, which is activated by a heterodimer of the cytokine IL-23p19 and the soluble cytokine receptor IL-12p40 [113]. IL-23 has been shown to be pro-inflammatory, but its role in cancer is less clear [113,114]. Like IL-12, IL-23 was overexpressed in EOC, with a positive correlation for overall survival [109]. However, TNFR-mediated enhancement of EOC growth was also shown to positively correlate with levels of IL-23 and IL-23R [115]. Moreover, polymorphisms in the IL-23R gene have been associated with late stage EOC in a Chinese population, suggesting a role in disease susceptibility [116]. One mechanism of action by which IL-23R signaling might mediate these effects is through expansion of Th17 cells.

4.7. G-CSFR

G-CSF is a secreted 25 kDa glycoprotein that binds to a homomeric single-chain receptor, G-CSFR, which is closely related to GP130 [38]. G-CSFR is expressed on a range of hematopoietic cells, such as mature neutrophilic granulocytes, myeloid progenitors, hematopoietic stem cells, monocytes and lymphocytes, as well non-hematopoietic tissues, including cardiomyocytes, neuronal precursors, endothelial cells and placental tissue [117]. Its principal role is in the G-CSF-induced mobilization of hematopoietic stem cells and production of neutrophils during "emergency hematopoiesis" [118]. These properties have seen G-CSF commonly used in the clinic to increase the production of neutrophils in patients with chemotherapy-induced neutropenia [119].

The G-CSFR has previously been implicated in a diverse range of malignancies. This includes hematological cancers, particularly acute myeloid leukemia [117], but also solid tumors. For example, a significant proportion of invasive bladder carcinomas have been shown to express both G-CSF and G-CSFR, with subsequent autocrine signaling contributing to their proliferation and survival in vitro (possibly via STAT3), as well as the size of their induced tumors in vivo [120]. G-CSF has also been demonstrated to stimulate the proliferation and migration of tumor cells derived from patients with head and neck squamous cell carcinoma, which could be blocked with neutralizing antibodies. Interestingly, while G-CSFR-positive tumors grew at a slower rate, they showed increased invasion, angiogenesis and survival [121]. Functional G-CSFR complexes have also been identified on a variety of other solid tumors [122].

The role of G-CSF/G-CSFR signaling in ovarian cancer has remained controversial. Broad expression of the G-CSFR has been reported in ovarian cancer cells, with co-expression of G-CSF often observed in these cells, or in neighboring stromal tissue, meaning both autocrine and paracrine activation is possible [123–126]. However, the clinical significance of G-CSF expression remains unclear, with one study showing it was an adverse prognostic factor if part of a paracrine loop [125], but another suggesting it did not correlate with prognosis [127]. G-CSF has been shown to support proliferation in some primary ovarian cancer cells and cell lines [123,128], but in others it inhibited proliferation [128] or had no effect [125,126,129]. G-CSF was found to enhance EGF-mediated mitogenesis in the G-CSFR-positive cell line OVCAR-3 [125], suggesting possible cross-talk with growth factor receptor signaling. We have recently demonstrated a role for G-CSF/G-CSFR signaling in EOC cell migration and survival, including in response to chemotherapeutic agents [129], suggesting it may contribute to ovarian cancer progression via several mechanisms.

4.8. OBR

Leptin, a 16 kDa protein, signals via OBR [130]. Like G-CSFR, OBR signals directly as a homodimer [131], but initiates similar signaling pathways to other IL-6R family receptors, namely the JAK–STAT, MAPK and PI3K pathways [132]. However, there exist multiple forms of the OBR with different signaling properties [133]. OBR functions in the regulation of energy metabolism, appetite, bone formation and angiogenesis [39]. However, it also has important roles in cancer cell proliferation, invasion and metastasis, including of breast, prostate, hepatic and endometrial cancers [134–137]. In the case of breast cancer, there have been extensive studies on leptin-induced cell proliferation [138,139] and epithelial-to-mesenchymal transition (EMT) [140]. The reported pro-proliferative and anti-apoptotic effects of leptin in prostate and breast cancers are mediated via STAT3 activation [141,142].

The role of leptin/OBR signaling in ovarian cancer remains less clear. Both leptin and its receptor are expressed in normal ovaries [143]. Overexpression of OBR represents a poor prognostic factor for epithelial ovarian cancer [144], but the mechanistic details are limited. For example, OBR was found to be expressed in three ovarian cancer cell lines, SKOV-3, BG-1 and OVCAR-3, but only the BG-1 cell line showed an increased rate of proliferation in response to leptin [145]. However, another study showed leptin could stimulate cell proliferation and inhibit apoptosis in the OVCAR-3 cell line [146]. Recent studies have confirmed that leptin can stimulate cell growth and inhibit apoptosis in OVCAR-3 cells through increased Cyclin D1 and Mcl-1 expression, in this case via the activation of the MAPK and PI3K signaling pathways [147]. Leptin has also been shown to contribute to the activation of the estrogen receptor pathway in ovarian cancer cells, thereby indirectly promoting tumor cell growth [148]. Interestingly, while the short forms of OBR were shown to be expressed in all EOCs, expression of the signaling-competent long receptor form was more variable [145], which may explain some of the observed variation in leptin responses.

5. Targeting IL-6R family signaling in epithelial ovarian cancer

5.1. Pathway inhibitors

Aberrant activation of IL-6R family members has been reported to play a major role in tumorigenesis [40]. In addition, JAK1/2 and STAT3 have been separately implicated in cancers and other proliferative disorders [43]. As a result, a number of specific therapeutics targeting the IL-6R–JAK1/2–STAT3 pathway are in clinical trials, including for EOC (Fig. 4).

5.1.1. IL-6 and IL-6R antibodies

Antibodies have been developed that specifically target either IL-6 or the IL-6R to block their activity, and shown to inhibit tumor growth either alone or in combination with cytotoxic chemotherapies in a range of carcinomas. For example, an anti-IL-6 antibody (CNTO-328, Siltuximab) has been used in a number of phase I/II clinical trials, including myeloma, renal, breast and prostate cancer [58,149–153]. Siltuximab inhibited IL-6-induced STAT3 induction in paclitaxel-resistant ovarian cancer cells [154], and decreased IL-6 signaling, tumor growth, angiogenesis and TAM generation in a xenotransplantation model, with evidence of efficacy in ovarian cancer patients [75]. An anti-IL-6R antibody (Tocilizumab), which inhibits ligand binding, has been demonstrated to be efficacious in rheumatoid arthritis [155], and represents an additional therapeutic option for ovarian cancer therapy. Finally, a soluble GP130 fusion (sgp130Fc) that blocks IL-6 trans-signaling reduced ascites formation and enhanced texane sensitivity of ovarian cancer xenografts [85].

5.1.2. JAK1/2–STAT3 inhibitors

JAK1/2 and STAT3 inhibitors have been developed and used in clinical trials particularly for myeloproliferative disorders and cancers

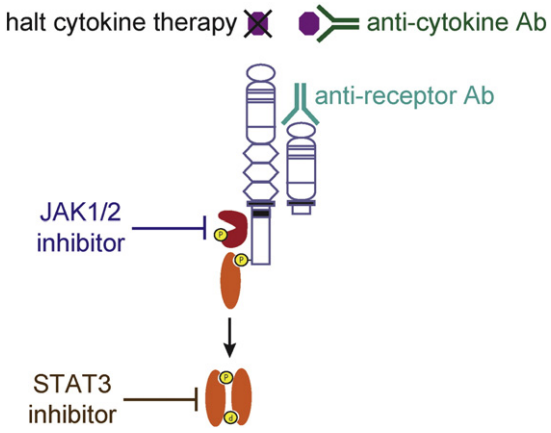

Fig. 4. Strategies for targeting IL-6R family signaling in ovarian cancer. A variety of therapeutic approaches are available to block the potential pathologic action of IL-6R family members in ovarian cancer, including cessation of cytokine therapy, antibodies to ligands/receptors, and inhibitors of the JAK1/2–STAT3 pathway.

[156–160]. Indeed, these have already shown success in ovarian tumors. Inhibition of JAK2 with diindolylmethane induced apoptosis in ovarian cancer cells [161], while the JAK inhibitor AZD1480 was able to increase the chemosensitivity of ovarian cancer cells lines by inhibiting STAT3 activation by IL-6 and oncostatin M [162]. The STAT3 inhibitor CDDO-Met was able to block IL-6 secretion and STAT3 activation in EOC cell lines, and down-regulate the anti-apoptotic proteins BCL-2 and BCL-XL in paclitaxel-resistant lines [163]. Similarly, curcumin was able to suppress both STAT3 activation and growth of EOC cells through up-regulation of the STAT3 inhibitor PIAS-3 [164]. Inhibition of STAT3 with siRNA was able to reduce growth and induce apoptosis of EOC cells [165], and reversed paclitaxel resistance in drug resistant cancer cell lines [166]. This collectively supports the notion that targeting the JAK/STAT pathway will also be efficacious in chemoresistant ovarian cancer. Recent studies have revealed the involvement of the JAK–STAT pathway in 'cancer stem-like cells' [167], making the use of such inhibitors even more enticing, as it may eliminate the cell population that facilitates the development of recurrent tumors. Finally, STAT3 inhibitors can indirectly reduce tumorigenicity by acting on non-cancer cells, such as decreasing angiogenesis through its effects on endothelial cell migration [43,168], or by abrogating tumor cell-mediated inhibition of DC maturation [169]. Thus, JAK1/2-STAT3 pathway inhibitors hold promise as a future therapeutic target in ovarian cancer.

5.2. Cytokine therapies in ovarian cancer

The important roles played by the IL-6R family have seen their respective cytokines become widely-used clinically. However, of particular relevance are their roles in cancer therapy. Thus, LIF has been administered to manage chemotherapy-induced peripheral neuropathy [170], IL-6 used as part of photodynamic therapy [171], while G-CSF has been extensively employed to aid hematopoietic recovery following chemotherapy for a range of cancers, including those of an ovarian nature [172]. However, if the cancer expresses the relevant receptor, these treatments may contribute to tumor development by switching on various signaling pathways that could lead to altered phenotypes, including increased proliferation, migration, survival and chemosensitivity [126]. Of particular relevance, G-CSF is commonly used in the context of ovarian cancer to restore neutrophils ablated by standard chemotherapeutic drugs used to treat patients [173]. Therefore, pre-screening patients for the presence of G-CSFR expression prior to administration of G-CSF should be considered, potentially indicating alternative approaches for these patients. Of relevance, a phase II trial showed that the co-administration of carboplatin, with granulocyte-macrophage colony stimulating factor and recombinant interferon gamma 1b in women with recurrent ovarian cancer elicited a response rate comparable with standard approaches [174], which might be useful alternative in the case of G-CSFR positive ovarian cancer.

6. Conclusions

IL-6R family members play important roles in the etiology of epithelial ovarian cancer. Several (e.g. IL-6R, LIFR, G-CSFR) can function directly in ovarian cancer cells, enhancing proliferation, migration/invasion and/or survival, including chemoresistance. Some can act to modify immune cell responses against EOC, either in a positive (e.g. IL-12, IL-23) or negative (e.g. IL-6) manner, or can influence endothelial cells to promote angiogenesis or alter their permeability (e.g. IL-6). Downstream signaling via STAT3 plays a central role in mediating these effects. This suggests some caution should be given to the use of some potentially deleterious cytokine-based immune therapies, such as G-CSF, with screening for the presence of the cognate receptor a useful potential step forward in the cases. However, the further development of other cytokine-based approaches, such as IL-12 and IL-23, should be encouraged. Finally, the clear elucidation of common pro-tumorigenic roles provides significant opportunities to develop strategies targeting IL-6R family signaling components, including inhibitors of STAT3 activation/function, in this disease setting.

Acknowledgements

The authors recognize the support of a Deakin University International Postgraduate Scheme Award (to JK) and funding from both the Geelong Community Foundation and Atkins Charitable Trust (to ACW).

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