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

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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.

Contents

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

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

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

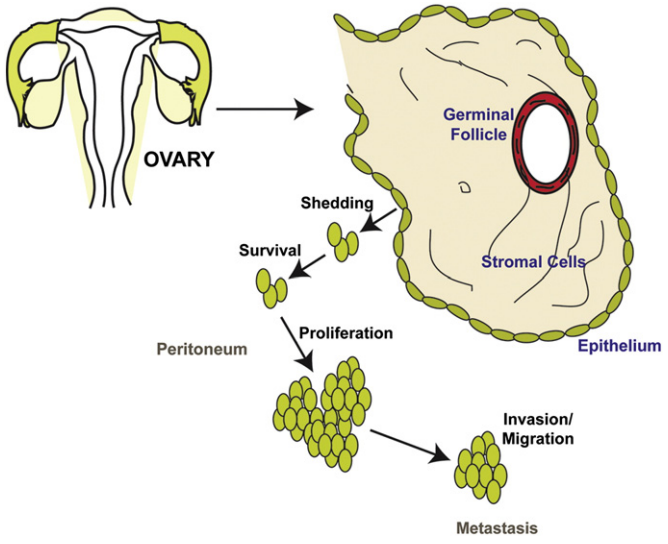

Fig. 1. Biology of ovarian cancer and its progression. Diagrammatic representation of the cell origins of ovarian cancers: germinal, stromal and epithelial. The progression of epithelial ovarian cancer is demonstrated in more detail, including the role of some key cancer phenotypes, which include proliferation,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