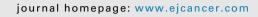


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Review

Targeting the tumour microenvironment in ovarian cancer



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KEYWORDS

Ovarian cancer; Tumour microenvironment **Abstract** The study of cancer initiation, growth, and metastasis has traditionally been focused on cancer cells, and the view that they proliferate due to uncontrolled growth signalling owing to genetic derangements. However, uncontrolled growth in tumours cannot be explained solely by aberrations in cancer cells themselves. To fully understand the biological behaviour of tumours, it is essential to understand the microenvironment in which cancer cells exist, and how they manipulate the surrounding stroma to promote the malignant phenotype.

Ovarian cancer is the leading cause of death from gynaecologic cancer worldwide. The majority of patients will have objective responses to standard tumour debulking surgery and platinum-taxane doublet chemotherapy, but most will experience disease recurrence and chemotherapy resistance. As such, a great deal of effort has been put forth to develop therapies that target the tumour microenvironment in ovarian cancer. Herein, we review the key components of the tumour microenvironment as they pertain to this disease, outline targeting opportunities and supporting evidence thus far, and discuss resistance to therapy. © 2015 Elsevier Ltd. All rights reserved.

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1. Introduction

1.1. Background

The study of cancer initiation, growth, and metastasis has traditionally been focused on cancer cells. This view postulates that cancer cells proliferate due to uncontrolled growth signalling pathways owing to derangements in both oncogenes and tumour suppressor genes [1]. However, despite the significant contributions of these pathways in the metastatic transformation of cells, the uncontrolled growth that occurs in tumours cannot be explained solely by aberrations in the cancer cells themselves. Tumours are complex tissues composed of tumour cells, as well as stroma consisting of blood and lymphoid vessels, nerves, fibroblasts and extracellular matrix proteins, endothelial cells, pericytes, and immune cells [1]. These collectively comprise the tumour microenvironment. To fully understand the biological behaviour of tumours, it is essential to consider the context in which cancer cells exist, and how they manipulate and are manipulated by the surrounding stroma to promote the malignant phenotype [2].

1.2. Epidemiology

Ovarian cancer is the second most common gynaecologic malignancy but is the most common cause of death from gynaecologic cancer worldwide [3,4]. Epidemiology, treatment and prognosis vary greatly by histopathologic subtype. Epithelial ovarian carcinoma comprises approximately 85 percent of ovarian malignancies [5,6], with high-grade serous (HGSC) being the most common histology.

While HGSC was historically thought to arise from the ovarian surface epithelium, contemporary paradigms suggest that other sources are more likely. Studies examining the distal, fimbriated end of the fallopian tubes in patients with serous carcinoma classified as either ovarian, fallopian tube or primary peritoneal in origin demonstrated that approximately 50% of patients had tubal intraepithelial carcinoma (TIC) present [7]. This suggests that TIC may be the precursor lesion and an important initiating factor in pelvic serous carcinoma [8]. Cells in the hilum of the ovary may be an alternative source of stem cells [9] and may have increased susceptibility to malignant transformation [9]. The primary mode of spread of HGSC was traditionally thought to be continuous exposure of the peritoneal surfaces to exfoliated tumour cells, however, there is evidence pointing to haematogenous mode of spread being an important component of the metastatic process [10,11]. Ovarian cancer cells have tropism for the omentum, which is likely mediated by a variety of factors produced by omental adipocytes [12].

Herein, we review the key components of the tumour microenvironment as they pertain to ovarian cancer, discuss targeting opportunities for individual stromal cell types as well as their prognostic potential, and outline emerging areas of research. Emphasis will be placed on fibroblasts, endothelial cells, and the immune components of the tumour microenvironment.

2. Cancer-associated fibroblasts

2.1. Background

Fibroblasts are the principal cellular component of connective tissue and are largely responsible for its maintenance and regeneration. The functions of fibroblasts include production and deposition of types I, III and V collagen and fibronectin, which are key components the fibrillar extracellular matrix [13], as well as synthesis of basement membrane proteins laminin and type IV collagen [14]. In addition, fibroblasts have an important role in the turnover and maintenance of the extracellular matrix by producing proteases such as matrix metalloproteinases [14]. Importantly, fibroblasts are crucial components in the process of wound healing, whereby they localise to wounds, generate extracellular matrix proteins, and aid in the contracture of the lesions that they occupy [13,15]. Additionally, these fibroblasts gain contractile strength [16] by expressing characteristically increased levels of α -smooth muscle actin (α -SMA) [13]. This phenomenon is mediated by growth factors such as transforming growth factor $-\beta$ (TGF- β) [17,18]. Once the wound has completed healing, activated fibroblasts undergo apoptosis [19,20].

The importance of fibroblasts in tumour development is well established. Initial studies showed that injection of carcinogenic Rous sarcoma virus in chickens led to development of tumours [21]. Tumours have been described as 'wounds that do not heal' [22]. Similarly, cancer cells have the ability to induce a reactive fibroblast phenotype, termed cancer-associated fibroblasts (CAF). CAFs are similar to activated fibroblasts in that they express α -SMA, but do not undergo apoptosis and do not lose their activated phenotype [23]. In addition, they express fibroblast activation protein (FAP) [15]. The interaction between cancer cells and fibroblasts in the tumour microenvironment is complex. CAFs can initially restrict tumour progression, similar to the relationship between cancer cells and immune components of the microenvironment [24]. However, CAFs eventually become activated by growth factors such as TGF-B1, platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and interleukin-6 (IL-Vascular endothelial growth factor (VEGF), 6). described in detail in the following section, is released by cancer cells and induces an influx of fibroblasts and thus, an increase in both the volume of tumour stroma

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