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Review

Ovarian cancer: Ion channel and aquaporin expression as novel targets of clinical potential

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Abstract Ovarian cancer is associated with limited overall survival, due to problems in early detection and therapy. Membrane ion channels have been proposed to play a significant, concerted role in the cancer process, from initial proliferation to metastasis, and promise to be early, functional biomarkers. We review the evidence for ion channel and aquaporin expression and functioning in human ovarian cancer cells and tissues. *In vitro*, K^+ channels, mainly voltage-gated, including Ca^{2+}-activated channels, have been found to control the cell cycle, as in other cancers. Voltage-gated, volume-regulated and intracellular Cl^- channels have been detected *in vitro* and *in vivo* and shown to be involved in proliferation, adhesion and invasion. Evidence for 'transient receptor potential', voltage-gated sodium and calcium channels, which have been shown to contribute to pathogenesis of other carcinomas, is also emerging in ovarian cancer. Aquaporins may be involved in cell growth, migration and formation of ascites via increased water permeability of micro-vessels. It is concluded that functional expression of ion channels and their regulation by steroid hormones and growth factors are an integral part of ovarian cancer development and progression. Furthermore, ion channels may be involved in multidrug resistance, commonly associated with treatment of ovarian cancer. We propose that

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ion channel studies can facilitate our understanding of the pathobiology of ovarian cancer and, ultimately, can serve as viable novel targets for its clinical management.

1. Introduction

Among gynaecological malignancies, ovarian cancer (OvCa) is the leading cause of death with a reported 5-year survival in the West of about 36%.[1] Often remaining undetected until a late stage, it is commonly referred to as the 'silent killer'. The poor prognosis associated with OvCa can be attributed to advanced stage at presentation and frequent resistance to chemotherapy. The disease is characterised by few and unspecific early symptoms and screenings so far have remained largely unsuccessful. Thus, the majority of women with epithelial OvCa are diagnosed with stage III-IV disease, when the cancer will already have spread to the upper abdomen.[2–4] Epithelial-mesenchymal transition, an important feature of metastatic progression, occurs in OvCa[5] and circulating tumour cells have also been detected in blood of patients.[6] Furthermore, lymphatic spreading[7] and brain metastasis can occur as late manifestations of OvCa.[8,9]

Although cancers classed as 'ovarian' are remarkably heterogeneous (with some derived from non-ovarian tissues), most arise from the ovarian surface epithelium.[10] Malignant cells may be shed into the peritoneal fluid where they aggregate and implant on the walls of the peritoneal cavity and invade other pelvic organs (Fig. 1). Ascites are formed frequently and their volume correlates with poor prognosis.[11]

The most important determinants of survival in OvCa are the stage of disease at diagnosis and the amount of residual disease remaining following initial surgery.[12] Thus, early detection and effective therapy are of utmost importance. In recent years, considerable progress has been made in identifying biomarkers of OvCa. The most commonly used serum marker is the carcinoma antigen-125 (CA125) which has proven of some use in detecting OvCa and tracking response to chemotherapy. Prospective studies have demonstrated that both CA125 and trans-vaginal ultrasound can detect a significant proportion of OvCa cases.[13–15] However, major problems remain in the clinic and, so far, no benefit in overall survival has been observed using CA125-based screening strategies. While women with OvCa often do have an elevated level of CA125, the reverse is not always true, and some women with the disease never manifest raised levels of antigen. In fact, many other conditions also can cause increased CA125 expression, including diverticulitis, endometriosis, liver cirrhosis, uterine fibroids, even normal menstruation and pregnancy.[16] Although some other biomarkers (including HE4, mesothelin and nidogen-2[17–19] and microRNAs[20,21]) have been proposed and new strategies for marker identification are being developed[22,23], a recent comparative study still found CA125 to be the most optimal.[24]

As regards therapy, despite the best available primary treatment, based mainly upon platinum-based drugs, the majority of advanced-stage patients relapse and die due to progressive disease. Consequently, there is significant unmet need (i) to improve sensitivity and specificity of OvCa detection, (ii) to develop new, ideally non-toxic, drugs to enable long-lasting, effective therapies and (iii) to overcome resistance to existing drugs.[25,26]

Recently, ion channels have emerged as novel biomarkers and pharmacological targets for human cancers and may even correlate with the main hallmarks of the

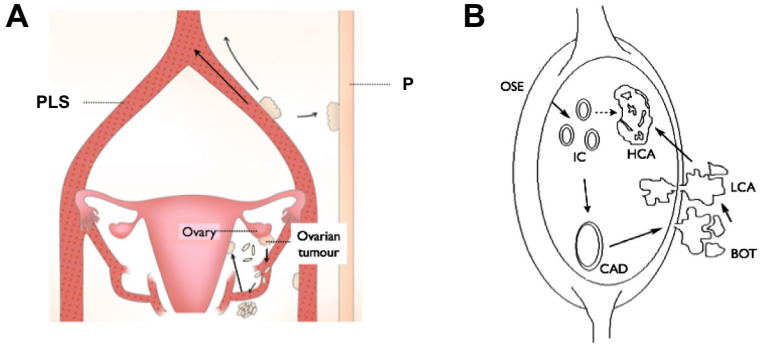

Fig. 1. Models of ovarian cancer progression.[5,210] (A) Initially, malignant cells are shed from the primary tumour into the peritoneal (ascetic) fluid from where they can disseminate throughout the abdominal cavity (as individual cells or tumour spheroids). Then, these cells can attach to and invade the peritoneum (P) and/or the pelvic lymphatic system (PLS). The latter may be followed by extravasation into distant organs such as lung or liver. Spread to other distant sites may also occur via blood circulation, although this type of metastasis is rare in ovarian cancer. (B) A model of cancer progression within the ovary proposed originally by Shih and Kurman.[211] Ovarian surface epithelial (OSE) cells initially dedifferentiate into inclusion cysts (IC) which may progress, sequentially, into cystadenoma (CAD), borderline ovarian tumour (BOT), low-grade carcinoma (LCA) and high-grade carcinoma (HCA). Inclusion cysts can also progress directly to HCA. This model involving OSE cells applies to 60% of ovarian cancer cases. Modified from Vergara et al.[5].