CHAPTER 3
PACE4 GENE EXPRESSION IN HUMAN OVARIAN CANCER

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Abstract: Aberrant proprotein convertase (PC) activity is associated with human tumorigenesis. We recently determined that paired basic amino acid converting enzyme 4 (PACE4) expression is greatly reduced in metastatic human ovarian cancer cells compared to normal ovarian cells. Reduced PACE4 expression is due to epigenetic modification of the PACE4 promoter, and PACE4 expression can be stimulated in ovarian cancer cells by treatment with demethylating agents and histone deacetylase inhibitors. Stable PACE4 re-expression in ovarian cancer cells produces cellular senescence or reduced survival. Preliminary evidence from PACE4 mutant mice strongly suggest that loss of PACE4 production results in ovarian abnormalities, including reduced fertility, premature loss of follicle structures, and abnormal cell morphology with features reminiscent of ovarian tumors.

Keywords: Ovarian cancer, PACE4, proprotein convertase, methylation, histone deacetylation

1. PROPROTEIN CONVERTASES AND TUMOR CELL MALIGNANT PHENOTYPES

The proprotein convertase (PC) family of serine endoproteases plays a vital role in normal cellular physiology by converting proproteins to biologically active molecules. We have determined that one member of the human PC family, PACE4, is expressed in normal ovarian surface epithelial (OSE) cells, however this expression is greatly reduced in epithelial ovarian cancer (EOC) cells. We hypothesize that loss of PACE4 expression plays a role in development of human ovarian cancer.

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2. BIOLOGY OF EPITHELIAL OVARIAN CANCER (EOC)

In this chapter we will restrict our discussion to EOC and will not discuss ovarian germ cell tumors or stromal tumors, which occur less frequently than EOC. EOC is comprised of five distinct histological subtypes (serous, clear cell, endometrioid, mucinous, and transitional) with serous adenocarcinomas occurring most frequently (Figure 1).

There is considerable debate regarding the origin of EOC, but it is believed that greater than 90% of ovarian tumors arise from the cells covering the surface of the ovary, the OSE (Figure 2; [1–4]). Our inability to conclusively ascribe the cellular origins of EOC stems from the fact that the etiology of ovarian cancer is poorly understood; there are currently no screening methods to detect ovarian cancer at an early stage of development.

Unlike many other human cancers, mouse models of human EOC have not been developed until recently [5–9]. A model of ovarian adenocarcinoma has been described in laying hens (Gallus domesticus) greater than 2 years of age [10], and spontaneous ovarian tumors can arise in some strains of mice [11] and rats [12]; however, these models show low tumor incidence and long latency periods, making them unattractive for experimental manipulation.

Evidence from human ovarian tissue samples suggests that OSE cells may become trapped within the ovarian cortex and form inclusion cysts (Figure 2C). Stratified cells that have lost their polarity and become dysplastic are often found in the inclusion cysts and may be a contributing factor in cancer formation [1, 13–15]. The OSE is usually separated from the stroma by a basement membrane comprised of laminin and collagen IV [16]. Epithelial cells on the ovarian surface are typically simple cuboidal (Figure 2A) or columnar (Figure 2B), whereas inclusion cysts are often lined with ciliated columnar epithelial cells that are not separated by a basement membrane and are in direct contact with stromal cells.

Current knowledge fails to explain the unique histological growth patterns of the different ovarian tumor subtypes. While direct experimental evidence defining factors that may contribute to OSE transformation are only now being identified, epidemiological evidence shows a correlation between increased parity and lactation, or oral contraceptive use for greater than 5 years, with a decreased risk of ovarian cancer. After ovulation the OSE divides and migrates to repair the wound left by the ovulated follicle. OSE cells may become encapsulated in the stroma and develop as inclusion cysts. Parity, lactation, and use of oral contraceptives coincide with reduced ovulation and a relatively quiescent OSE, thus reducing the chances of cyst formation. It remains unclear what factors influence the transformation of the OSE in the inclusion cysts, but one possibility is that these cells, once encased in the ovarian stroma, are subjected to a greater concentration of extracellular signaling molecules that may increase their chances for neoplastic transformation. While this has been a generally accepted theory for the cellular origin of ovarian cancer, this line of reasoning is compromised by the occurrence of ovarian cancer after prophylactic oophorectomy. Further research is required to ascertain if ovarian cancers may arise from cells such as fallopian tube or endometrial epithelium.