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Review

Genetically engineered mouse models for epithelial ovarian cancer: Are we there yet?

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ABSTRACT

The development of preclinical spontaneous genetically engineered mouse models (GEMMs) requires an understanding of the genetic basis of the human disease. Such robust models have proven invaluable for increasing understanding of human malignancies as well as identifying new biomarkers and testing new therapies for these diseases. While GEMMs have been reported for ovarian cancer, the majority have proven disappointing overall in their recapitulation of paired genetic and histological features especially for serous ovarian epithelial cancer. This review describes GEMMs for ovarian cancer, in particular, high grade serous ovarian cancer and assesses these in light of recent changes in our understanding of the human malignancy.

Contents

Abbreviations: EOC, epithelial ovarian cancer; SEOC, serous EOC; EEOC, endometrioid EOC; OSE, ovarian surface epithelium; GEMM, genetically engineered mouse model; CRE, Cre recombinase; fl, floxed; LSL, loxP-STOP-loxP; CMV, cytomegalovirus; STIC, tubal *in situ* cancer with *TP53* mutation; rtTA, tetracycline-dependent reverse transactivator; TRE, tetracycline-responsive element; ADCRE, a replication deficient advenovirus altered to express CRE under the control of the CMV promoter; GCT, granulosa cell tumors; NAD, no tumors detected; LS, leiomyosarcoma; S, sarcoma; CIS, carcinoma *in situ*; Hyp, hyperplasia; EEC, endometrioid endometrial cancer; LH, luteinising hormone; FSH, follicle stimulating hormone.

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TP53	tumor protein p53
BRCA1/2	breast cancer 1/2, early onset gene
PTEN	phosphatase and tensin homolog
RB1	retinoblastoma 1
ARID1A	AT rich interactive domain 1A (SWI-like)
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
CTNNB1	catenin, β1
HNF1	HNF1 homeobox A
KRAS	Kirsten rat sarcoma viral oncogene homolog
ERBB2	v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2
BRAF	v-raf murine sarcoma viral oncogene homolog B
AMH/MIS	anti-Mullerian hormone/Mullerian-inhibiting substance
AMHR2/MISIIR	anti-Mullerian hormone receptor 2/Mullerian-inhibiting substance receptor 2
SV40	simian vacuolating virus 40 oncogene
SV40Tag	small t and large T antigens
Ogp	oviductal glycoprotein 1
Osp-1	ovarian specific promoter-1
Pax8	paired box 8
Stk11	serine/threonine kinase 11 (Lkb1)
Fshr	follicle stimulating hormone receptor
Cyp-19	cytochrome P450, family 19, subfamily a, polypeptide 1
Pgr	progesterone receptor
Apc	adenomatosis polyposis coli
PTTG	pituitary tumor transforming gene

1. Introduction

1.1. Ovarian cancer

Ovarian cancer is the 7th most common cancer diagnosed in women worldwide, accounting for 4% of all cancers in women [1]. Approximately 90% of ovarian cancers are epithelial in origin and these are further divided according to the histopathological features of the tumor. The majority (70%) of epithelial ovarian cancers (EOCs) are high-grade or Type II serous EOC (SEOC) [2]. These present as moderately or poorly differentiated late stage, highly aggressive neoplasms that spread rapidly and are associated with poor outcome. The other major histopathological EOC subtypes are endometrioid (high and low grade, or Type I and Type II) accounting for 10% of EOC, clear cell (10%), low grade serous (<5%) and mucinous (3%), with the remainder being undifferentiated, mixed or borderline malignant [2].

Table 1
Molecular aberrations associated with different EOC subtypes [10–12].

Epithelial ovarian cancer subtype	Genes with molecular aberrations
High grade serous (Type II)	*TP53*, *BRCA1/2*, *RB1*
Endometrioid (Type I/II)	*PTEN*, *ARID1A*, *PIK3CA*, *CTNNB1*
	TP53 (high grade/Type II only)
Clear cell (Type I)	*HNF1*, *ARID1A*, *PIK3CA*
Mucinous (Type I)	*KRAS*, *ERBB2*
Low grade serous (Type I)	*BRAF*, *KRAS*

Up until the early 2000s the site of origin for all EOC subtypes was thought to be the single layer of epithelial cells lining the ovary (ovarian surface epithelium; OSE) [3]. However, broader analyses of molecular and histopathological features of benign as well as EOC tissues led to the findings that a significant proportion of mucinous EOC may be metastases from the colon rather than primary ovarian carcinomas [4,5], and that endometrioid and clear cell EOC may arise from atypical endometriosis [6,7]. Similarly, the site of origin for high grade SEOC has also come into question, with the secretory cells in the fimbrial end of the fallopian tube now thought to be a major or significant site of origin for SEOC [8,9].

Molecular genetic analysis of these cancers has identified different molecular genetic features and pathways of tumorigenesis for the different subtypes (Table 1). Notable is that *TP53* loss or mutation of *TP53* is virtually pathognomonic for high grade SEOC [11]. Rare cases of *TP53* mutated high grade endometrioid EOC (EEOC) have been reported and their reclassification as SEOC is being considered [13,14]. Other aberrations documented by The Cancer Genome Atlas for high grade SEOC included alteration of the homologous repair pathway in 51% of cases, with *BRCA1/2* silencing or mutation found in 33% of these cases; RB signaling alterations in 67% of cases with loss or mutation of *RB1* contributing to 10% of these alterations; and altered PI3K/RAS signaling in 47% of tumors with mutation or loss of *PTEN* in 7% and amplification or mutation of *PIK3CA* or *KRAS* in 18% and 11% of tumors, respectively [11]. When taken together, the changing views of the site of origin and the different genetic features of each subtype has led to the notion that the different subtypes are fundamentally distinct diseases (reviewed in [14]). Indeed, while all subtypes involve the ovaries, whether they are all in fact "ovarian cancers" is now in debate.

1.2. Mouse models of ovarian cancer

There is a paucity of robust genetically engineered mouse models (GEMMs) for EOC. Given the changes in our understanding of the origins and genetic features of the different subtypes, this may well be expected as the design of GEMMs requires prior knowledge of both of these aspects of the malignancy. Technical issues compound this changing knowledge; the most significant being the difficulty in specifically and exclusively targeting changes to cells of origin for

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