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Review

Homologous recombination deficiency and ovarian cancer

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Abstract The discovery that PARP inhibitors block an essential pathway of DNA repair in cells harbouring a BRCA mutation has opened up a new therapeutic avenue for high-grade ovarian cancers. BRCA1 and BRCA2 proteins are essential for high-fidelity repair of double-strand breaks of DNA through the homologous recombination repair (HRR) pathway. Deficiency in HRR (HRD) is a target for PARP inhibitors. The first PARP inhibitor, olaparib, has now been licensed for BRCA-mutated ovarian cancers. While mutated *BRCA* genes are individually most commonly associated with HRD other essential HRR proteins may be mutated or functionally deficient potentially widening the therapeutic opportunities for PARP inhibitors. HRD is the first phenotypically defined predictive marker for therapy with PARP inhibitors in ovarian cancer. Several different PARP inhibitors are being trialled in ovarian cancer and this class of drugs has been shown to be a new selective therapy for high-grade ovarian cancer. Around 20% of high-grade serous ovarian cancers harbour germline or somatic BRCA mutations and testing for BRCA mutations should be incorporated into routine clinical practice. The expanded use of PARP inhibitors in HRD deficient (non-BRCA mutant) tumours using a signature of HRD in clinical practice requires validation.

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1. Introduction

Until recently, the treatment of ovarian cancer has not been adapted to histological or biological variability in the tumour. Surgery and platinum–taxane chemotherapy remain the cornerstone of primary treatment followed at recurrence by further platinum-based chemotherapy until the tumour becomes 'platinum-resistant.' It is now clear that epithelial ovarian cancer (EOC) comprises several different diseases [1,2]. The collective term represents a distinct and diverse group of molecularly and aetiologically distinct pathologies with differing clinical behaviour (Fig. 1). If the outcome of advanced ovarian cancer is to improve then our approach to treatment and the development of novel agents must target and exploit distinct subgroups within this heterogeneity.

Around 70% of EOC are high-grade serous adenocarcinomas. A defining feature of this subtype is the presence of mutations within the tumour suppressor gene *p53* [3,4]. In addition, molecular analysis of high-grade serous ovarian cancer (HGSOC) by The Cancer Genome Atlas (TCGA) has shown that around half have aberrations in homologous recombination repair (HRR), a critical DNA damage response pathway [5]. Repair of DNA damage following platinum-based therapy has long been considered an important determinant of tumour chemosensitivity. Several genetic lesions causing homologous recombination deficiency (HRD) include germline and somatic BRCA mutations as well as mutations of genes such as *ATM*, *CHEK2*, *RAD51* and *MRE11A* (Table 1), and epigenetic silencing has been described in HGSOC. Exploitation of HRD by inhibitors of PARP (poly ADP ribose polymerase) a DNA repair enzyme involved in base-excision repair producing further disruption of DNA damage repair has formed the basis of a new molecularly targeted therapeutic strategy to treat ovarian cancer [6]. Over the last decade, studies with inhibitors of DNA repair, specifically PARP inhibitors in BRCA-mutated ovarian cancers have resulted in truly personalized medicine in ovarian cancer.

Here we review the central role of HRD in broadening the application of PARP inhibitors as

Table 1
Mutational frequency of non-BRCA HRR genes.

HR-pathway gene	Observed frequency, all epithelial ovarian cancer (%)	Observed frequency, high-grade ovarian cancer (%)	Reference
RAD51C	0.41–2.9	1.9	[48,70–72]
RAD51D	0.35–1.1	0.95	[3,48,72]
RAD51B	0.06	0.95	[3,72]
RAD50	0.2	–	[70]
RAD54L	–	0.5	[61]
ATM	0.8–0.86	0.32–1.0	[3,48,70]
BRIP1	0.9–1.72	0.32–1.0	[3,48,73]
CHEK2	0.4–1.6	0.32–1.0	[3,48,70]
FANCA	–	0.5	[61]
FANCI	–	0.5	[61]
NBN	0.2–0.25	0.63–1.0	[3,48,70,73]
PALB2	0.2–0.5	0.63	[3,48,73]

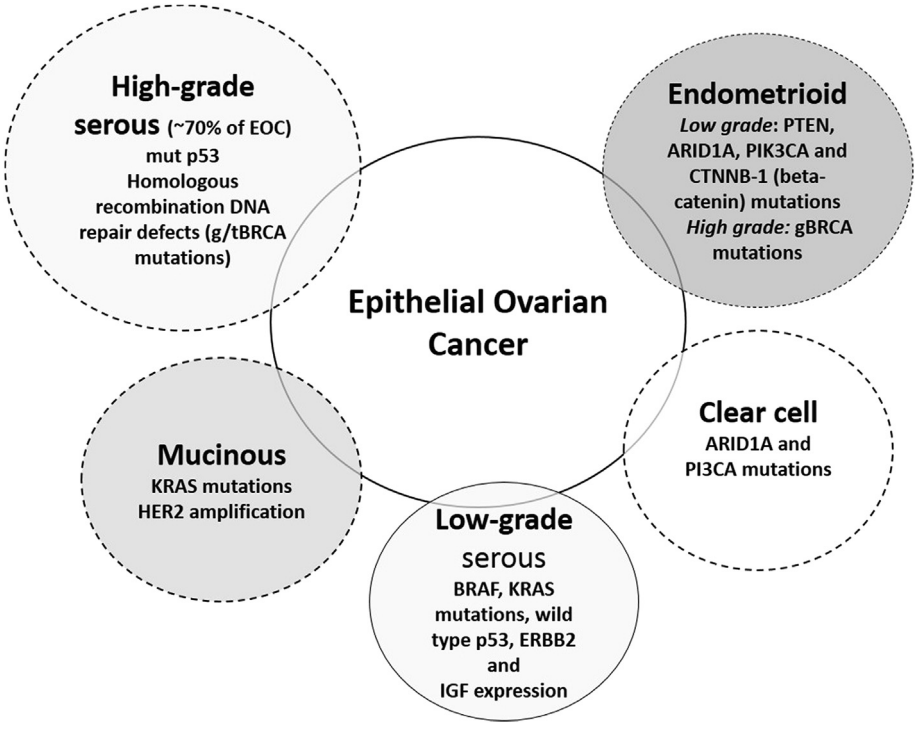

Fig. 1. Histological and molecular sub-types of epithelial ovarian cancer (EOC). g, germline, t, tumour.