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Ovarian cancer: Status of homologous recombination pathway as a predictor of drug response

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ABSTRACT

Epithelial ovarian cancer (EOC), particularly high-grade serous subtype, is associated with germline mutations in *BRCA1/BRCA2* genes in up to 20% of the patients. BRCA1/BRCA2 proteins are important components of the homologous recombination (HR) pathway, a vital DNA repair process that protects the genome from double-strand DNA damage. Recent studies revealed frequent somatic mutations of *BRCA1/BRCA2* and hypermethylation of the promoter of *BRCA1* in EOC, in addition to germline mutations. Comparison of DNA copy number changes in tumors with or without *BRCA1/BRCA2* alterations, lead to the identification of several signatures that detect HR pathway defects, here named "HRness". These signatures predict platinum-sensitivity and survival in EOC, as it was previously shown for germline mutations of *BRCA1/BRCA2*. They are currently investigated in clinical trials as potential predictive biomarker for response to poly(ADP- ribose) polymerase inhibitors.

1. Introduction

Ovarian cancer (OC) is the second most frequent gynecological cancer and the leading cause of death from a gynecological cancer among European women, with an estimated 42,700 deaths in 2012 (Ferlay et al., 2013). It comprises a large array of histologic, biological and genetic features, and is usually divided into three groups: epithelial malignancies which represent the most common type (90%), stromal tumors and germ cell tumors (Morgan et al., 2014). According to a recent classification based on their histology, molecular biology and natural history (Kurman and Shih Ie, 2011), epithelial ovarian carcinomas (EOC) can be further subdivided into two broad categories. Type I tumors consist of low-grade serous, endometrioid, clear cell, mucinous and transitional carcinomas.

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They are typically present as large masses that are confined to one ovary (stage Ia), are indolent, generally cured by surgery alone and they demonstrate low chemosensitivity. Type II tumors account for the majority of EOC (75%) and include high-grade serous ovarian carcinomas (HGSOC), undifferentiated carcinomas and carcinosarcomas. They are of high histological grade, are diagnosed at advanced stage (III/IV) and show good chemosensitivity but poor outcome.

At the molecular level, type II tumors are characterized by frequent alterations of DNA damage pathways. DNA damage repair can be divided into pathways that repair damage of one of the DNA strands (mismatches, bulky adducts, single-strand break) or damage that affects both DNA strands (crosslinks, double-strand breaks (DSBs)) (Vollebergh et al., 2012). In the presence of DSBs, repair systems no longer depend on the complementary strand for correct repair. Depending on the phase of cell cycle, DSBs are repaired either by non-homologous end joining (NHEJ) which takes place in G0-G1 phase and is error-prone or by homologous recombination (HR), which takes place in the S or G2 phase and is error-free (Vollebergh et al., 2012). HR pathway (which includes breast cancer susceptibility gene 1 (BRCA1) and BRCA2) appears to be the major mechanism for protecting the integrity of the genome in proliferating cells (Roy et al., 2012). It repairs DSBs by using the homology of the sister chromatid as a template. Fanconi anemia (FA) is a rare recessive inherited genomic instability disorder, caused by mutations in genes regulating replication-dependent removal of DNA inter-strand crosslinks (ICLs) (Moldovan and D'Andrea, 2009). FA pathway (which includes BRCA2) has functional overlap with HR pathway.

In this review, we will focus on genes that play an important role in DNA repair process (Roy et al., 2012; Pennington et al., 2014), and whose germline mutations are associated with increased risk of EOC. We will describe their involvement in HR pathway and their impact on response to DNA damaging agents, namely platinum, alkylating agents and poly(ADP-ribose) polymerase (PARP) inhibitors.

2. Molecular pathogenesis of epithelial ovarian cancer

Types I and II EOC have distinct molecular profiles reflecting different disease entities. Type I EOC are genetically stable, characterized by different mutation profiles depending on the histological subtype. For instance, low grade serous EOC show frequent somatic mutations of the MAPKinase pathway genes (*KRAS* and *BRAF*), whereas endometriosis-associated (clear cell and endometroid) carcinomas have mutations of *ARID1A*, *CTNNB1* and *PIK3CA*. Finally, mucinous OC are characterized by mutations of *KRAS*, *BRAF* and *RNF43*. Type I EOC are supposed to arise from corresponding benign cystadenomas, often through borderline (low malignant potential) tumors, supporting the classical paradigm of stepwise morphologic progression during tumorigenesis (Morgan et al., 2014). This hypothesis is supported by molecular biology data, as mutations of the same genes have been found in early lesions as well as invasive carcinomas, suggesting that such alterations occur early in the evolution of type I EOC.

HGSOC account for the majority of type II EOC. Their main molecular characteristic is mutation of the tumor suppressor gene *TP53* in virtually all cases (Vang et al., 2016; Cancer Genome Atlas Research N, 2011). They display high level of genomic instability shown by the high number of copy number alterations (Cancer Genome Atlas Research N, 2011; Kuo et al., 2009). They rarely display the gene mutations found in type I tumors. The second most frequent mutated genes in HGSOC are *BRCA1* and *BRCA2* with germline and/or somatic mutations occurring in 20% of the cases (Cancer Genome Atlas Research N, 2011). The histopathological characteristics of *BRCA*-linked OCs differ from the spectrum associated with their sporadic counterparts: among the *BRCA* mutation carriers, HGSOC are overrepresented, although endometrioid and clear cell histologies are also observed (Walsh et al., 2011). However, tumors of mucinous histology do not occur in the *BRCA* mutation carriers (Morgan et al., 2014). In the last decade, reports of early lesions in the Fallopian tubes (FT) named serous tubal *in situ* carcinomas (STICs) harboring similar *TP53* mutations with their corresponding serous carcinomas suggest a tubal origin of HGSOC (review in Karst and Drapkin (2011); Perets and Drapkin (2016)).

3. DNA damage and homologous recombination (HR)

One aspect of maintaining genomic integrity is mediated by a cellular network of signaling events named DNA damage response (DDR) that is triggered in response to genotoxic stress. Different DNA damage repair mechanisms exist, as resumed in Table 1 (Roco et al., 2014; Camps et al., 2007). Small base adducts are repaired by a mechanism named base excision repair (BER). Bulkier single-strand lesions that distort the DNA helical structure, such as those caused by ultraviolet, are processed by nucleotide excision repair (NER) (Lord and Ashworth, 2012). DNA DSBs are considered to be the most threatening form of DNA damage, as the integrity of both strands of the DNA duplex is compromised simultaneously (Roy et al., 2012; Caestecker and Van de Walle, 2013). The major mechanisms that cope with DSBs are NHEJ and HR. HR is the most accurate DSBs repair mechanism, of which the absence can lead to gross genome rearrangements and hence genomic instability. HR acts mainly during the S and G2 phases of cell cycle and it tends to restore the original DNA sequence to the damaged site. It removes part of the DNA sequence around the DSB, and uses the DNA sequence on a homologous chromatid as a template for the synthesis of new DNA at the site of damage (Lord and Ashworth, 2012). Upon DNA damage, the MRE11-RAD50-NBS1 complex (MRN) binds the ends of DSBs sites and recruits the DNA damage kinase ataxia-telangiectasia mutated (ATM), followed by ataxia telangiectasia and Rad3-related (ATR) activation. Then, the signal is mediated by CHEK2 and BRCA1, and leads to initiation of repair by the effectors BRCA2 and RAD51. There are also several facilitators of the HR pathway, such as PALB2 and BRIP1 (review in Roy et al. (2012)). In contrast to HR, NHEJ occurs in G0-G1 phases of cell cycle. It mediates repair by directly ligating the ends of DSBs together. Sometimes this process can cause deletion or mutation of DNA sequences at or around the DSB site (Lord and Ashworth, 2012). Thus, NHEJ can often be mutagenic when compared to HR and is considered as error-prone. Finally, translesion synthesis (TLS) and template switching allow DNA to continue to replicate in the presence of DNA lesions that would otherwise halt the process (Lord and Ashworth, 2012).

The core DDR machinery does not work alone but is coordinated with a set of complementary mechanisms that are crucial to maintaining the integrity of the genome (Lord and Ashworth, 2012). The main function of FA pathway seems to be the coordination of three classical DNA repair pathways, namely NER, TLS and HR, in response to DNA ICLs (Moldovan and D'Andrea, 2009). To this end, the FA pathway employs a unique nuclear protein complex, named FA core complex, that ubiquitinates FANCD2 and FANCI, leading to formation of DNA repair structures (Moldovan and D'Andrea, 2009). Some members of the FA pathway are not required for FANCD2-I ubiquitination and appear to function downstream the repair process such as FANCD1, better known as BRCA2 (Howlett et al., 2002), FANCJ (BRIP1) and FANCN (PALB2). Those 3 genes are also involved in HR pathway. Importantly, germline and somatic mutations of genes involved in HR/FA pathway, mainly *BRCA1*/*BRCA2*, and rarely *PALB2, BRIP1, RAD51* and *CHEK2,* are observed in EOC patients (Cancer