European Journal of Cancer 86 (2017) 5–14

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

EJC Biennial Report

Genomic signatures as predictive biomarkers of homologous recombination deficiency in ovarian cancer☆

Adriaan Vanderstichele [a,b,*], Pieter Busschaert [a,b], Siel Olbrecht [a,b], Diether Lambrechts [c,d], Ignace Vergote [a,b]

[a] *Department of Gynaecology and Obstetrics, University Hospitals Leuven, Belgium*
[b] *Division of Gynaecological Oncology, Leuven Cancer Institute, KU Leuven, Leuven, Belgium*
[c] *Center for Cancer Biology, VIB, Leuven, Belgium*
[d] *Laboratory for Translational Genetics, Department of Oncology, KU Leuven, Leuven, Belgium*

Received 22 August 2017; accepted 24 August 2017

KEYWORDS
Ovarian cancer;
Double-strand breaks;
DNA repair;
Homologous recombination;
Alternative end joining;
Non-homologous end joining;
PARP inhibitor;
Whole-genome sequencing;
Mutational signatures

Abstract DNA repair deficiency is a common hallmark of many cancers and is increasingly recognised as a target for cancer therapeutics. Selecting patients for these treatments requires a functional assessment of multiple redundant DNA repair pathways. With the advent of whole-genome sequencing of cancer genomes, it is increasingly recognised that multiple signatures of mutational and chromosomal alterations can be correlated with specific DNA repair defects. The clinical relevance of this approach is underlined by the use of poly-(ADP-ribose) polymerase inhibitors (PARPi) in homologous recombination (HR) deficient high-grade serous ovarian cancers. Beyond deleterious mutations in HR-related genes such as BRCA1/2, it is recognised that HR deficiency endows ovarian cancers with specific signatures of base substitutions and structural chromosomal variation. Multiple metrics quantifying loss-of-heterozygosity (LOH) events were proposed and implemented in trials with PARPi. However, it was shown that some of the HR-deficient cases, i.e. CDK12–mutated tumours, were not associated with high LOH-based scores, but with distinct patterns of genomic alterations such as tandem duplication. Therefore, more complex signatures of structural genomic variation were identified and quantified. Ultimately, optimal prediction models for treatments targeting

☆ This work was supported by the Belgian Cancer Plan Action 29 of the Ministry of Healthy of Belgium (grant number KPC-29-054), by the Vriendtjes tegen Kanker fund (grant number EVO-FOVTK1-O2010), by The Flemish League against Cancer (grant number EVO-ZKD0344) and by Flanders Innovation & Entrepreneurship (grant number AIO 155009).

* *Corresponding author*: Adriaan Vanderstichele, University Hospitals Leuven, Department of Gynaecology and Obstetrics, Herestraat 49, 3000, Leuven, Belgium.
E-mail address: adriaan@vanderstichele.eu (A. Vanderstichele).

http://dx.doi.org/10.1016/j.ejca.2017.08.029

Rearrangement signatures

DNA repair will need to integrate multiples of these genomic signatures and will also need to assess multiple resistance mechanisms such as genomic reversion events that partially or fully re-activate DNA repair.

1. Introduction

DNA repair deficiency confers cancer susceptibility and represents a common feature of carcinogenesis, as it drives malignant transformation with the accumulation of genomic alterations in cancer cells [1]. Conversely, the presence of multiple, partially redundant, DNA repair pathways provides a compensating mechanism for cancer cells to avoid non-viable amounts of genotoxic stress [2]. Selectively targeting these compensating DNA repair pathways constitutes a therapeutic approach founded upon 'synthetic lethality' [3]. This concept was validated through encouraging results with poly-(ADP-ribose) polymerase inhibitors (PARPi) in high-grade serous ovarian cancer (HGSOC), where a majority of cases are characterised by defective double-strand DNA break repair by homologous recombination (HR) [4]. Inhibition of the PARP1/2 enzymes increases the demand for HR-directed repair and shifts DNA repair towards alternative error-prone repair pathways such as non-homologous end joining (NHEJ), eventually leading to cellular lethality [5] (refer Fig. 1).

To leverage DNA repair defects as targets for cancer therapeutics, it is of key importance to know which DNA repair components still remain functional at a specific time point during the course of disease. Regarding HR pathway defects in HGSOC, previous efforts have mainly focused on the detection of bi-allelic inactivations of HR-pathway genes by germline and somatic deleterious mutations and on promoter DNA hypermethylation [6,7]. Clinical successes with PARPi [8–10] clearly provided rationale for the detection of high-penetrance inactivating BRCA1/2 mutations as predictive biomarkers in over 20% of epithelial ovarian cancers [11]. Inactivating mutations in multiple other, mostly moderately penetrant, HR-pathway genes (e.g. *RAD51C*, *RAD51D*, *BRIP1* and the *FANC* group of genes) occur at low frequencies and response data are currently insufficient for most variants to confirm predictive significance [12]. Moreover, it is estimated that over one-third of HR-deficient ovarian cancers cannot be characterised by (epi)genetic assessment of HR-pathway genes [4,11].

Therefore, alternative approaches using metagene signatures [13] and functional assays [14,15] were proposed. Despite the interesting idea of capturing the HR deficiency phenotype downstream of the genomic level, these assays lack clinical validation and suffer from practical issues impeding clinical implementation.

An alternative generic approach has been based on the analysis of so-called 'genomic scars'. Throughout its lifetime, the genome of a cancer cell acquires a panoply of genomic alterations as a result of various biological mutational processes, each involving an endogenous or exogenous DNA damage and associated DNA repair event [16]. These processes each leave their characteristic trace in the genome, under the form of accumulating somatic mutations and chromosomal structural variation. The detection and quantification of these genomic scars, reflective of ongoing or historical DNA repair deficiencies, are now proposed as predictive biomarkers for cancer therapeutics targeting DNA repair. In this review, we provide a specific overview of the current knowledge on genomic signatures in the HGSOC genome indicative of defective DNA repair by HR.

2. Double-strand break repair in HR-deficient ovarian cancer

Patterns of genomic structural and mutational variation arise on a background of defective DNA repair. In this context, double-strand breaks (DSBs) represent the most determining lesions because they interfere with the physical continuity of the genome. Tumour-specific deficiencies in regulators and effectors of DSB repair have a major influence on the genomic architecture of cancer cells.

Essentially, three pathways are responsible for repair of DSBs: repair by HR, NHEJ or alternative end joining (Alt-EJ) (see Fig. 1).

DNA end resection at the DSB is critical for DNA repair pathway choice, as it is necessary for HR and Alt-EJ–mediated DNA repair. Briefly, the broken DNA ends are resected from 5′ to 3′ in two steps—an initial end clipping of 20bp, followed by an extensive resection—to generate long stretches of 3′ single-stranded DNA tails. End resection is dependent on the cell cycle phase and occurs after DNA replication, when homologous strands are available for homology directed repair. Indeed, in the S/G2 phase, cyclin-dependent kinases (CDKs) promote end resection by phosporylating CtIP, which is essential for the assembly of the MRN resection complex (MRE11/RAD50/NBS1), coordinated by the BRCA1 protein. When end resection occurs, DSBs can be further repaired through error-free HR DNA repair by the recruitment of BRCA2 and the effector RAD51 to construct nucleoprotein filaments that catalyse the recombination between the broken strand and its undamaged homologue. On the other hand, the end-protecting factors 53BP1 and REV7 restrict end resection but are inactivated by CDKs in the S/G2 phase of the cell cycle. When this suppression is