Gynecologic Oncology 132 (2014) 506–512

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review

Mismatch repair deficiency in ovarian cancer — Molecular characteristics and clinical implications ☆

Xue Xiao, David W. Melton, Charlie Gourley *

University of Edinburgh Cancer Research UK Centre, MRC Institute of Genetics and Molecular Medicine, Western General Hospital, Crewe Road South, Edinburgh, UK

HIGHLIGHTS

- Both mutational and expression data suggest that MMR deficiency is more common in non-serous ovarian cancer than in serous subtypes.
- The effect of MMR deficiency on ovarian cancer chemosensitivity remains unproven but synthetic lethal approaches offer hope of novel therapies.

ARTICLE INFO

Article history:
Received 7 October 2013
Accepted 2 December 2013
Available online 10 December 2013

Keywords:
Ovarian cancer
HNPCC
Mismatch repair deficiency
Synthetic lethality

ABSTRACT

DNA mismatch repair (MMR) deficiency is associated with increased risk of developing several types of cancer and is the most common cause of hereditary ovarian cancer after *BRCA1* and *BRCA2* mutations. While there has been extensive investigation of MMR deficiency in colorectal cancer, MMR in ovarian cancer is relatively under-investigated. This review summarizes the mechanism of MMR, the ways in which MMR deficiency can promote carcinogenesis in general and then assesses the available studies regarding MMR deficiency in ovarian cancers with specific emphasis on implications for disease incidence and therapy. The incidence of germline MMR gene mutations in ovarian cancer is only 2% but other mechanisms of gene inactivation mean that loss of expression of one of the seven main genes (MSH2, MSH3, MSH6, MLH1, MLH3, PMS1 and PMS2) occurs in up to 29% of cases. Both mutational and expression data suggest that MMR deficiency is more common in non-serous ovarian cancer. Some studies suggest an improved survival for patients with MMR deficiency compared to historical controls but these do not account for the preponderance of non-serous tumors. A number of *in vitro* studies have suggested that MMR deficiency is a cause of platinum resistance. To date this has not been categorically demonstrated in the clinic. Larger studies that account for stage of presentation and immunohistochemical subtype are required to assess the effect of MMR deficiency on survival and chemosensitivity. Investigation of MMR related synthetic lethality in colorectal cancer has identified dihydrofolate reductase, DNA polymerase β and DNA polymerase γ and PTEN-induced putative kinase 1 as synthetic lethal to certain MMR defects by causing accumulation of oxidative DNA damage. These synthetic lethal targets require tested and others should be sought within the context of MMR deficient ovarian cancer in an attempt to provide novel therapeutic strategies for these patients.

Contents

☆ CG is supported by the Scottish Funding Council. The Edinburgh Ovarian Cancer Database is supported by Experimental Cancer Medicine Centre (ECMC) funding from the Scottish Chief Scientist's Office and Cancer Research UK. XX is supported by the China Scholarship Council and the Nicola Murray Foundation.

* Corresponding author at: University of Edinburgh Cancer Research UK Centre, MRC Institute of Genetics and Molecular Medicine, Crewe Road South, Edinburgh, UK. Fax: +44 1317773520.
E-mail address: charlie.gourley@ed.ac.uk (C. Gourley).

0090-8258/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ygyno.2013.12.003

Introduction

Epithelial ovarian cancer is the leading cause of gynecological cancer death in the developed world, with a lifetime risk of 1–2% [1]. The most common histological subtype is high grade serous (70%); other subtypes include endometrioid (10%), clear cell (5–10%), low grade serous (5%), mucinous (3%), and undifferentiated (1%) [2–7]. Over 60% of ovarian cancer patients are diagnosed with advanced stage disease (spread beyond the pelvis) with an associated five year survival rate of 20–30% [1]. In contrast, for patients with stage I ovarian cancer, the five year survival rate is around 90% [1].

The most significant risk factor for ovarian cancer is family history which depends on the number of first and second degree relatives with ovarian or breast cancer and their age at diagnosis [8]. Hereditary germline mutations are estimated to account for 10% to 20% of all ovarian cancers [9–11]. *BRCA1* and *BRCA2* germline mutations are associated with an 11% to 40% risk of developing the disease [12] and account for 65–85% of all inherited cases [13–15]. Hereditary non-polyposis colorectal cancer (HNPCC), which is caused by mutations in genes that are responsible for DNA mismatch repair (MMR), is the next most common cause of hereditary ovarian cancer, and accounts for 10% to 15% of all cases of hereditary ovarian cancer [13,16].

Many studies have investigated MMR deficiency in colorectal cancer, leading to defined clinical guidelines for detecting HNPCC kindred, identification of unique clinical and pathological features of these tumors and a greater understanding of the molecular pathogenesis of colorectal cancer. However, MMR deficiency in ovarian cancer is relatively under-investigated. This review summarizes the mechanism of MMR, the ways in which MMR deficiency can promote carcinogenesis in general and then assesses the available studies regarding MMR deficiency in ovarian cancers with specific emphasis on implications for disease incidence and therapy.

The mismatch repair system

The MMR system plays an important role in maintaining genomic stability. It recognizes and corrects biosynthetic errors that arise during DNA replication [17] as well as mispaired bases that are generated during recombination or caused by oxidative DNA damage [18]. MMR therefore reduces DNA errors 100–1000 fold, and prevents them from becoming fixed mutations during cellular proliferation.

MMR has been extensively studied in *Escherichia coli*, and human MMR proteins have been discovered based on their homology to *E. coli* proteins [17]. Seven proteins including three MutS-homologs (MSH2, MSH3 and MSH6), and four MutL homologs (MLH1, MLH3, PMS1 and PMS2) are involved in human MMR [17,19].

DNA mismatch repair consists of three steps: recognition, excision and resynthesis (Fig. 1) [17]. MMR is initiated once MutS recognizes mismatched DNA and binds to it. The MutS homodimer is formed by either MSH2/MSH6 (the MutSα complex) or MSH2/MSH3 (the MutSβ complex). The MutSα complex recognizes single base mismatches and short insertion–deletion loops in the DNA, while the MutSβ complex recognizes larger loops [20]. Subsequently, MutLα (formed by MLH1 and PMS2) is recruited and it mediates the process from mismatch recognition by MutS to activation of downstream activities [21]. The endonuclease function in the PMS2 subunit is then activated by the mismatch and MutS complex and directs strand excision in a proliferating cell nuclear antigen (PCNA)-, replication factor C (RFC)-, and ATP-dependent process [22]. RFC loads PCNA onto the DNA helix and PCNA plays an important role in both excision and DNA repair synthesis [22,23]. Replication protein A (RPA) and Exonuclease 1 (Exo1) are also involved in the excision process, and Exo1 has been reported to function in both 3′and 5′-directed repair events [21,24]. PMS1 and MLH3 also dimerize with MLH1, but their role in DNA repair is less well understood [25]. High-fidelity replicative polymerases, Polδ or Polε, and DNA ligase 1 complete resynthesis of the strand [24].

MMR deficiency and cancer development

MMR deficiency leads to microsatellite instability

Defects of any of these MMR genes result in microsatellite instability (MSI) [26]. MSI is characterized by accelerated accumulation of single nucleotide mutations and altered length of microsatellite sequences [27]. Microsatellites, also known as short tandem repeats (STRs) and simple sequence repeats (SSRS) are short, repetitive sequences of DNA between one and six base pairs in length distributed throughout the genome [28]. The length of these repeats varies between individuals, but is constant within the cells of an individual, unless they have microsatellite instability. When MMR fails, DNA replication infidelity across these tandem repeats coupled with MMR deficiency results in the accumulation of mutations.

MSI can significantly affect cellular behavior and is associated with multi-step tumorigenesis, as instability at coding microsatellites in cancer-related genes can cause frameshift mutations and functional inactivation of corresponding proteins [29]. To date a number of genes involved in DNA repair, apoptosis, signal transduction, transcriptional regulation and immune surveillance [30] have been found mutated in cancers exhibiting MSI (Fig. 2). Mutated genes that provide selective growth advantage to cells lacking MMR function are considered as the driving force during MSI tumorigenesis and are termed real common target genes [29].

As a hallmark feature of HNPCC-associated cancers, MSI has been found in 90% of colorectal tumors from individuals with Lynch syndrome, and in 10% to 15% of sporadic colorectal tumors [31]. It also occurs in 75% of endometrial and up to 100% of ovarian cancers in patients from HNPCC families [31].

According to the uniform criteria developed by the National Cancer Institute (NCI), a panel of five independent genomic sites is recommended for microsatellite status analysis in colorectal cancer, including two mononucleotide repeats (Bat25 and Bat26) and three dinucleotide repeats (D2S123, D5S346, and D17S250). Tumors are termed high-frequency MSI (MSI-H) if two or more of the five loci exhibit variations in microsatellite sequence length (*e.g.* insertion/deletion mutations). If only one of the microsatellite sequences shows instability, the tumor is termed low frequency MSI (MSI-L). The tumor is classified as microsatellite stable (MSS), if no mutation has occurred in any of the five markers [27].

MMR deficiency can also be caused by promoter hypermethylation

As shown in Fig. 2, MMR dysfunction can be caused by both genetic and epigenetic mechanisms. In Lynch syndrome, MMR deficiency is a result of germline mutation of one of the 7 MMR genes, with MLH1 accounting for most cases. Somatic inactivation of the remaining wild-type allele can be caused by loss of heterozygosity, somatic mutation