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Review article

Epigenetic therapy for the treatment of epithelial ovarian cancer: A clinical review

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ABSTRACT

Despite a good initial response to chemotherapy, the majority of patients with epithelial ovarian cancer will eventually recur and die of their disease. The introduction of targeted therapies to traditional chemotherapy regimens has done little to improve overall survival in women with ovarian cancer. It has become increasingly apparent that the cancer epigenome contributes significantly to the pathogenesis of ovarian cancer and may play an important role in cell proliferation, metastasis, chemoresistance, and immune tolerance. Epigenetic therapies such as DNA methyltransferase inhibitors and histone deacetylase inhibitors have the potential to reverse these epigenetic changes; however, more research is needed to determine how to incorporate these agents into clinical practice. In this review, we discuss the common epigenetic changes that occur in epithelial ovarian cancer, the current epigenetic therapies that may target these changes, and the clinical experience with epigenetic therapy for the treatment of epithelial ovarian cancer.

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1. Introduction

With an estimated 22,280 new cases of ovarian cancer and 14,240 deaths projected in 2016, ovarian cancer remains the fifth-leading cause of cancer death in women (Siegel et al., 2016). While the majority of patients respond to primary platinum and taxane-based

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chemotherapy, recurrence rates are high with over 75% of patients ultimately relapsing (Ozols et al., 2003). Advances in cytotoxic chemotherapy and development of novel targeted therapies such as the poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors have improved progression-free survival (PFS) but have failed to significantly impact overall survival (OS) (Armstrong et al., 2006; Ledermann et al., 2012). As long-term prognosis for patients with epithelial ovarian cancer remains poor, there is a need for development of new therapies to augment or replace traditional cytotoxic chemotherapies. One such area of therapeutic potential involves the use of epigenetic therapy.

While germline and somatic mutations in tumor suppressor genes such as *BRCA1/2* have long been implicated in the development of ovarian cancer (Welcsh & King, 2001), it has become increasingly apparent that epigenetic changes also play a critical role. Epigenetic changes alter gene expression without affecting the underlying DNA sequence. The two most widely affected epigenetic pathways in cancer are DNA methylation and histone modification (Dawson & Kouzarides, 2012).

2. DNA methylation

DNA methylation occurs at the carbon-5 position of cytosine residues, usually in cytosine-phosphate-guanine (CpG) dinucleotide sequences, and inhibits gene transcription (Fig. 1). The process of DNA methylation is regulated by a family of enzymes known as the DNA methyltransferases (DNMTs), which consists of DNMT1, DNMT3a, and DNMT3b. DNMT1 maintains appropriate methylation between cell divisions, while DNMT3a and DNMT3b control *de novo* methylation during embryogenesis (Sarkar et al., 2013). Levels of all three DNMTs have been shown to be upregulated in cancer cells compared to normal cells (Kautiainen & Jones, 1986; Xie et al., 1999).

CpG islands are CpG-rich sequences associated with the promoters of widely expressed genes which are normally protected from methylation. Genome-wide mapping has confirmed that 5–10% of these CpG islands become abnormally methylated in cancer genomes, and this *de novo* methylation has been implicated in the silencing of multiple tumor suppressor genes, as well as other genes that are critical for regulation of cell growth, angiogenesis, and DNA repair (Dawson & Kouzarides, 2012).

A number of genes have been found to be silenced *via* hypermethylation in ovarian cancer, and the degree of abnormal methylation has been correlated with disease progression and decreased survival (Watts et al., 2008; Wei et al., 2002). *BRCA1* promoter hypermethylation with resultant decreased *BRCA1* protein expression has been identified in 15–35% of patients with sporadic ovarian cancer (Bai et al., 2014; Baldwin et al., 2000). The effect of *BRCA1* methylation on prognosis is unclear; it has been associated with improved survival in some studies and decreased survival in others (Bai et al., 2014; Chiang et al., 2006). *BRCA1* methylation has also been correlated with improved chemosensitivity and response to PARP inhibitors, suggesting that patients with *BRCA1* methylation have a similar phenotype to patients with germline *BRCA1* mutations (Chaudhry et al., 2009; Veeck et al., 2010). Hypermethylation has been found to contribute to silencing of multiple other tumor suppressor genes in ovarian cancer, including *p53, MLH1, HIC1, p16, E-cadherin,* and *APC* (Strathdee et al., 2001; Makarla et al., 2005; Chmelarova et al., 2013), and both hypermethylation of multiple genes and increased expression of DMNTs have been associated with the development of platinum resistance (Li et al., 2009; Matei & Nephew, 2010).

While ovarian cancer is characterized by hypermethylation of numerous promoter CpG islands, the ovarian cancer genome is hypomethylated as a whole (Watts et al., 2008). Hypomethylation of unstable satellite DNA sequences has been shown to play an important role in carcinogenesis and is thought to contribute to genomic instability (Feinberg & Vogelstein, 1983; Widschwendter et al., 2004). Patients with ovarian cancer have significantly increased hypomethylation of satellite DNA compared to patients with benign or borderline ovarian tumors, and this extensive hypomethylation is strongly correlated with advanced stage and poor prognosis (Watts et al., 2008; Widschwendter et al., 2004).

3. Histone acetylation

Histones are proteins that package DNA into nucleosomes which are the functional unit of chromatin. Post-translational histone modification can occur through several mechanisms; acetylation at the ε-amino group of lysine residues on the amino-terminal tails of the histone proteins is the best understood (Dawson & Kouzarides, 2012). Histone acetylation converts chromatin to an open or transcriptionally permissive state and is regulated by a class of enzymes known as histone acetyltransferases (HACs). Conversely, deacetylation is regulated by the histone deacetylases (HDACs) and converts chromatin to a more condensed or transcriptionally repressive state due to increase in electrostatic interactions between the histones and DNA (Fig. 2) (Dawson & Kouzarides, 2012). HDACs are also involved in acetylation of lysine residues of several non-histone proteins, including the estrogen and androgen receptors, p53, c-Myc, and STAT3 (Kim & Bae, 2011).

Eighteen distinct HDACs have been identified and separated into four classes based on sequence homology with yeast (Dawson & Kouzarides, 2012). Classes I, II, and IV are zinc-dependent, while class III is characterized by NAD+ dependence. Class I HDACs are found only in the nucleus and are the most prevalent, while class II, III, and IV HDACs are found both in the nucleus and cytoplasm (Kim & Bae, 2011).

High levels of HDACs with resultant histone hypoacetylation have been identified in multiple cancers (Nakagawa et al., 2007). HDAC1, 2, and 3 are all class I HDACs that are expressed at high levels in ovarian cancer and are associated with poor prognosis (Khabele et al., 2007; Weichert et al., 2008). Expression of the class I HDACs has been shown to increase in a stepwise fashion when moving from benign to borderline to malignant ovarian tumors, indicating that these HDACs may play an important role in carcinogenesis. Specifically, HDAC1 and 2 expression correlate with increased cell proliferation in ovarian cancer cells, while HDAC3 expression inversely correlates with E-cadherin expression, suggesting a role in cell migration and metastasis (Hayashi et al., 2010). Additionally, HDAC overexpression has been correlated with development of platinum resistance in ovarian cancer (Kim et al., 2012).

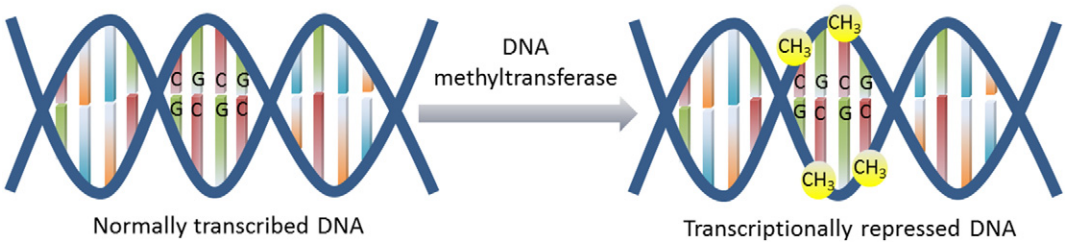

Fig. 1. The process of DNA methylation is mediated by a family of enzymes known as the DNA methyltransferases, which add a methyl (CH_3) group at the carbon-5 position of cytosine-phosphate-guanine (CpG) dinucleotide sequences. The addition of the methyl groups inhibits DNA transcription and can lead to silencing of various genes.