
Epigenetic Changes In Endometrial Cancer: An Important Area Of Research

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ABSTRACT

Endometrial cancer is the most commonly diagnosed gynaecological cancer. Based on differences in clinic pathologic characteristics, there are two subtypes of endometrial carcinoma Type 1 and Type 2. Multiple risk factors (Obesity, use of an intrauterine device, Age, Diet and Exercise, Type 2 Diabetes) are developing endometrial cancer. Likewise, epigenetics is the study of alteration gene and modulated gene expression with alteration in DNA sequences. In mammals, epigenetic modifications include DNA methylation, histone modifications, and miRNA.

Epigenetics alterations are associated with promoter methylation of DNA such as hMLH1 (MutL homolog1), hMSH2 (MutS homolog2), hMSH3, hMSH6 and hPMS2 and demethylation of tumor suppressor genes such as PTEN, RASSF1A, APC, HOPX, HOXA10, and MGMT. Promoter methylated genes (Phosphatase and tensin homolog, Ras association domain family 1 isoform, Antigen-presenting cell, Homeobox Only Protein Homeobox, Homeobox protein Hox-A10, O6 methylguanine DNA methyltransferase) are related to cell proliferation, development, and differentiation. This study concludes the effect of promoter hypermethylation of genes on genetic and epigenetic modifications and reveals how these genes can act as a biomarker and improve health outcomes.

INTRODUCTION

Endometrial cancer is the most commonly diagnosed gynaecological cancer. It is the 4th most common cancer in women [1]. Endometrial means that the cancer starts in the lining of the womb. This lining is called the endometrium. About 95% of endometrial cancers are adenocarcinomas. Adeno means that the cells that have become cancerous. They are the cells of glandular tissue. So, for the most common type of womb cancer, the cancer is in the glands of the endometrium. Based on differences in clinic pathologic characteristics, there are two subtypes of endometrial carcinoma. Type 1 cancers are the most common type. They are usually endometrioid adenocarcinomas. Type 2 cancers include uterine serous carcinomas and clear cell carcinomas. Type 1 cancers are linked to excess estrogen whereas Type 2 cancers are not linked to excess estrogen. Type I tumors are usually well-differentiated, and most patients present with early-stage of the disease and have a favourable prognosis. In contrast, type II, non-endometrioid endometrial carcinoma, is more common in older postmenopausal women, often poorly differentiated. Type I tumors commonly have near-diploid karyotypes, microsatellite instability and mutations in PTEN, K-RAS and CTNNB1 (β -catenin) genes; whereas type II tumors are characterized more often by p53 mutation, overexpression of Her-2/neu and an aneuploid karyotype[2]. Although multiple risk factors affect the risk of developing endometrial cancer, such as obesity, the use of an intrauterine device (IUD), age, hormone factors, estrogen therapy these factors have been identified the understanding of the etiologies of the two subtypes of endometrial cancer continues to evolve. Endometrial cancer is a complex disease driven by epigenetic alterations, abnormal genetic as well as environmental factors, as a common molecular alteration in human neoplasia, epigenetics is the study of heritable phenotype changes that do not involve alterations in the DNA sequence [3]. Epigenetic changes are equally responsible for genetic changes in the development and progression of cancer. Epimutation change can assist in determining whether factors controlling the production of macromolecules in particular cells are turned on or off [4].

These epigenetic processes are necessary which regulate the normal functions of the cell during all the stages, including development, differentiation and facilitate adaptation to environmental

changes, such as nutritional variation of exposure to cigarette smoke, chemicals, radiation, and hormones [5].

MECHANISM OF EPIGENETIC MODIFICATIONS

Epigenetic modifications can be defined as heritable alterations in gene expression and cellular function without changes to the original DNA sequence. The processes responsible for epigenetic regulation are DNA methylation, modifications in chromatin, and noncoding RNA (miRNA).

DNA Methylation

The DNA of most organisms is modified by a post-replicative process which results in three types of methylated bases in DNA: C5-methylcytosine, N4-methylcytosine, N6-methyladenine, this modification is called DNA methylation. It is an epigenetic mechanism used by cells to control gene expression. Some mechanisms exist to control gene expression in eukaryotes, but DNA methylation is a commonly used epigenetic signalling tool that can fix genes in the “off” position. Addition of methyl group to the C-5 position of cytosine residues. Most cytosine methylation occurs in the sequence context 5’CG3’. This occurs almost exclusively at cytosines that are followed immediately by a Guanine- CpG Dinucleotide. Methyl groups are transferred from S-adenosyl methionine in a reaction catalysed by DNA methyltransferases (DNMT) or methylases. SAM is then converted to SAH (S-adenosyl homocysteine).

Histone Modification

Histones are subject to a wide variety of posttranslational modifications including but not limited to, lysine acetylation, lysine and arginine methylation, serine and threonine phosphorylation and lysine ubiquitination and sumoylation. These modifications occur primarily within the histone amino-terminal tails protruding from the surface of the nucleosome as well as on the globular core region.

Histone modifications are proposed to affect chromosome function through at least two distinct mechanisms. The First mechanism suggests modifications may alter the electrostatic charge of the histone resulting in a structural change in histones or their binding to DNA. The Second

Mechanism proposes that these modifications are binding sites for protein recognition modules, such as the bromodomains or chromodomains, that recognize acetylated lysines or methylated lysine, respectively.

Mi RNAs

miRNAs represent small RNA molecules encoded in the genomes of plants and animals. These highly conserved 22 nucleotides long RNA sequences regulate the expression of genes by binding to the 3'-untranslated regions (3'-UTR) of specific mRNAs. A growing body of evidence shows that miRNAs are one of the key players in cell differentiation and growth.

PROMOTER HYPERMETHYLATION OF GENES IN ENDOMETRIAL CANCER

DNA mismatch repair gene in Endometrial Cancer.

Hereditary non-polyposis colorectal cancer (HNPCC), or Lynch Syndrome, is one of the most common familial cancer syndromes. The molecular basis for HNPCC is a defect in a DNA mismatch repair gene, usually a germline mutation in **hMLH1, hMSH2, hMSH3, hMSH6, and hPMS2**. A defective DNA mismatch repair causes microsatellite instability and, a high risk of the colon as well as endometrial cancers. The hMLH1 and hMSH2 mutations are rare (less than 10%) in sporadic endometrial cancers in comparison to the MSI+ phenotype. However, reduced protein expression of hMLH1 and other mismatch repair genes is a common finding in endometrial cancers. The study of these MMR proteins has revealed that recognition of the base-base mismatches and deletion/insertion loops is performed by a heterodimer of either MSH6 and MSH2 or MSH2 and MSH3. The MSH2 and MSH3 are heterodimers preferentially recognizes insertion and deletion loops. Consequently, cancers arising with a loss of MSH6 function display microsatellite instability.

A heterodimer of MLH1-PMS2 operates as a molecular matchmaker and is involved in executing the repair of mismatches. Promoter hypermethylation is associated with a lack of expression of hMLH1 in human cancers and mismatch repair-defective human tumor cell lines.

Methylation of steroid receptor genes in Endometrial Cancer.

Endometrium is highly responsive to hormonal stimuli. The cyclic production of estrogen and progesterone during the menstrual cycle, and declining sex steroid hormone levels after menopause are directly correlated with endometrial proliferation and morphological changes. There are several risk factors that directly or indirectly affected by estrogen. Several studies have been done, evaluated the association of promoter hypermethylation of the estrogen receptor (ER) and progesterone receptor (PR) genes in endometrial cancer.

Estrogen receptors (ERs) are group of proteins found inside the cells. Genes are located at chromosome 6q25.1, have a CpG island in its promoter and exon 1 regions. Commonly they are receptors but activated by the hormone estrogen. Two classes of ER are there, one is nuclear receptor family of intracellular and membrane estrogen and the other is, once activated by estrogen, the ER can translocate into the nucleus and perform the function of DNA binding. This is the proliferative phase of the endometrium. It strongly binds to SHBG and albumin.

Progesterone receptors (PR) is a secondary phase of the endometrium. It binds to corticosteroid-binding globulin and albumin. It is a nuclear receptor and protein found inside cells belong to subfamily 3, group C and member 3. It is encoded by a single PGR gene residing on chromosome 11q22 in humans. They are ligand-activated transcription factor members of the steroid hormone.

Methylation of tumor suppressor genes in endometrial cancer.

Promoter hypermethylation of tumor suppressor genes is a major event in the origin of many cancers. Some studies have been done and a list of tumor suppressor genes frequently hypermethylated in endometrial cancer are PTEN, RASSF1A, APC, HOPX, HOXA10, and MGMT.

PTEN

The phosphatase and tensin homolog (PTEN, also known as MMAC1/TEP1) gene on chromosome 10q23.3[5]. It provides instructions for making an enzyme. It is characterized as a tumor suppressor, which means that it regulates cell division by keeping cells from growing and dividing too rapidly or in an uncontrolled way. Promoter hypermethylation, as the alternative

mechanism of PTEN allelic inactivation and occurred in sporadic colorectal tumors with microsatellite instability [6].

RASSF1A

The Ras association domain family 1 isoform (RASSF1A) neoplastic genes were regulated like cell cycle suppression, programmed cell death and heredity instability that shows a vital role in suppressing Ras-mediated oncogenesis [7]. Moderation of each allele of a neoplasm inhibitor gene is necessary for carcinoma. RASSF1A is the most commonly hypermethylated neoplasm suppressor genes in human tumors and may assist as a biomarker for disease detection [8]. Natural compounds such as curcumin and resveratrol inhibit the activity of DNA methyltransferases.

APC

Adenomatous polyposis coli (APC), a tumor suppressor gene, regulates β -catenin in the Wnt signaling pathway [9]. It provides instructions for making a protein that keeps cells from growing and dividing rapidly in an uncontrolled manner. This helps to ensure the number of chromosomes in the cell is correct following cell division. APC gene promoter methylation has been observed around 20%-45% in endometrial cancer [10].

MGMT

The O6 methylguanine DNA methyltransferase (MGMT) is a polymer repair macromolecule that protects the human regulating from agents and tumor conduct of endogenous cancer [11]. Also, it induces protection to alkylating agents and removes alkyl adducts from the O6 position of guanine in DNA.

P16

The p16 gene also called CDKN2A, encodes p16INK4A that suppresses the CDK45: Cyclin and CDK6: cyclin D complexes [12]. Hypermethylation of the p16 neoplasm suppressor gene and has effects on transcriptional down-regulation or silencing, this has been shown as one of the vital structures of p16INK4a gene inactivation in varied kinds of carcinoma such as colon cancer, thyroid cancer, and cervical cancer [13].

RAR β 2

Retinoic Acid Receptor (RAR β 2) is known as a cancer inhibitor gene by correlating with retinoic acid. Expression of retinoic acid receptor β (RAR β) is defined to be absent or disease controlled in cancer [14]. Epigenetic silencing by promoter hypermethylation ends up in retinoic acid therapy failure in breast carcinoma [15].

CONCLUSION

Recent Advancements in the field of epigenetics, help in understanding the role of epigenetic alterations in normal cellular processes and abnormal changes leading to endometrial carcinogenesis. It has been observed that DNA methylation plays a key role in understanding the promoter hypermethylation of genes in endometrial cancer. By understanding the promoter hypermethylation of tumor suppressor genes, some of the epigenetic changes can be studied in endometrial cancer. Promoter hypermethylation of these genes can act as a biomarker. This can act as an important tool against endometrial cancer all over the world in the future.

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