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TET enzymes and 5hmC epigenetic mark: new key players in carcinogenesis and progression in gynecological cancers

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Abstract. – DNA methylation is an epigenetic mechanism involving the transfer of a methyl group onto the C5 position of the cytosine to form 5-methylcytosine (5mC). In general, DNA methylation in cancer is associated with the repression of the expression of tumor suppressor genes (TSG) and the demethylation with the overexpression of oncogenes. DNA methylation was considered a stable modification for a long time, but in 2009, it was reported that DNA methylation is a dynamic modification. The Ten-Eleven-Translocations (TET) enzymes include TET1, TET2, and TET3 and participate in DNA demethylation through the oxidation of 5mC to 5-hydroxymethylcytosine (5hmC). The 5hmC oxidates to 5-formylcytosine (5fC) and 5-carboxylcitosine (5caC), which are replaced by unmodified cytosines *via* Thymine-DNA Glycosylase (TDG). Several studies have shown that the expression of TET proteins and 5hmC levels are deregulated in gynecological cancers, such as cervical (CC), endometrial (EC), and ovarian (OC) cancers. In addition, the molecular mechanisms involved in this deregulation have been reported, as well as their potential role as biomarkers in these types of cancers. This review shows the state-of-art TET enzymes and the 5hmC epigenetic mark in CC, EC, and OC.

Key Words:
Gynecological cancers, DNA methylation, DNMT enzymes, TET enzymes, 5- hydroxymethylcytosine, Epigenetics.

Introduction

DNMT1, DNMT3A, and DNMT3B proteins are canonical members of the DNA methyltransferases (DNMTs) family with enzymatic activity, while DNMT2 and DNMT3L proteins are noncanonical members of this family without enzymatic activity. DNMT1 is a DNMT enzyme of maintenance, while DNMT3A and DNMT3B are DNMTs enzymes *of novo*[1,2]. DNMTs are enzymes that catalyze the addition of a methyl group from S-adenosyl-L-methionine (SAM or AdoMet) to the C5 position of cytosine nucleotides (5-methylcytosine or 5mC), followed by guanine nucleotides (known as CpG) in DNA[3,4]. Rich regions in CpG dinucleotides are called CpG islands and are located mainly in gene promoters. In general, the methylation in CpG islands is associated with transcriptional repression; for instance, the abnormal methylation in the pRB Tumor Suppressor Gene (TSG) promoter is associated with its transcriptional silencing in human cancers[5,6]. DNA methylation was considered a relatively stable modification[7,8] until 2009, when it was shown that DNA methylation is a dynamic modification that involves the participation of another modification on DNA, known as 5-hydroxymethylcytosine (5hmC)[9,10].

The 5hmC was identified for the first time in bacteriophages in 1952[11]. In mammals, this mo-

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dified cytosine was observed in tissue samples from the brain and liver of rats, mice, and frogs in 1972[12]. Later, the presence of 5hmC in Purkinje and Granule neurons from the murine cerebellum was reported in 2009[9]. At the same time, it was reported that the TET1 enzyme catalyzes the oxidation of 5mC to 5hmC[10]. On the other hand, it was reported that TET2 and TET3 enzymes also catalyze the oxidation of 5mC to 5hmC[13,14]. Alterations in the *TET1* gene were discovered in 2003, and it was observed to TET1 as a fusion partner on chromosome 10q22 with the *MLL* gene on chromosome 11q23, resulting in Ten-Eleven chromosomal Translocation t (10,11) (q22, q23) in rare cases of acute myeloid and lymphocytic leukemias[15,16]. Similarly, *TET2* and *TET3* alterations were discovered in myeloproliferative neoplasms in 2009[17-19].

DNA abnormal methylation is a common event in several human diseases, such as human cancers[20-22]. Alterations in DNA demethylation are critical events in carcinogenesis, tumor progression, and resistance to treatment in human cancers, including gynecological cancers. This review summarized the state-of-art of TET enzymes and 5hmC in cervical (CC), endometrial (EC), and ovarian (OC) cancers.

Structure of TET Enzymes

TET1 gene is located in the 10q21 human chromosome region, contains 12 exons, and encodes a protein of 2,136 amino acids (aa)[23]. TET1 proteins have an isoform due to the use of an alternative promoter, known as TET1^{ALT}, which has 1,472 aa and lacks the CXXC domain; however, it retains its catalytic activity[24]. *TET2* gene is located in the 4q24 human chromosome region, contains 11 exons, and encodes a protein of 2,002 aa. TET2 protein (known as isoform 1) has two short isoforms (1,165 and 1,194 aa, respectively) due to alternative splicing; however, only isoform 1 has catalytic activity[17,18,23,25]. Moreover, the TET2 protein isoform 1 lacks the CXXC domain; however, a phylogenetic and chromosome neighborhood analysis identified the *CXXC4* gene (also known as the *IDAX* gene) in the opposite orientation to the *TET2* gene. *CXXC4* gene encodes to the CXXC domain of TET2, which is separated by 650 kb and transcribed in the opposite orientation from the *TET2* gene, suggesting that a local chromosomal inversion separated the CXXC domain from the *TET2* gene[26]. *TET3* gene is located in the 2p13 human chromosome region, contains 11 exons, and encodes a protein of 1,795 aa[23,27] (Figure 1).

TET proteins have a common CXXC zinc finger domain at the amino-terminal region and a conserved catalytic domain (CD) that consists of a cysteine (Cys) rich region and a Double-Stranded β-Helix (DSBH) domain at the carboxyl-terminal region. Specifically, the DSBH domain contains eight conserved anti-parallel β strands with a highly conserved His-Xaa-Asp-(Xaa) n-His motif (Xaa is any aa) and a conserved Arg aa that binds the Fe (II) and 2-oxoglutarate (OG) cofactors. Two zinc fingers bring the DSBH domain and Cys-rich region to form a compact catalytic domain[26,28] (Figure 1).

Action Mechanism of TETs Enzymes

TET1, TET2, and TET3 enzymes are members of the TET family, which are Fe (II) and 2-OG dependent methylcytosine dioxygenases[10,13,14]. TET enzymes participate in "active" and "passive" DNA demethylation (Figure 2). In "active" DNA demethylation, TET proteins catalyze the oxidation of 5mC to 5hmC[10,13,14]. 5hmC is converted to 5-formylcytosine (5fC) by TET enzymes-mediated oxidation, subsequently, the 5fC is oxidate to 5-carboxylcytosine (5caC)[29]. Finally, 5fC and 5caC are excised by Thymine-DNA glycosylase (TDG), generating abasic sites, which are replaced by unmodified cytosines through the Base-Excision Repair (BER) pathway[30-32]. In "passive" DNA demethylation, TET enzymes convert 5mC to 5hmC, which is poorly recognized by the UHRF1/DNMT1 complex; thus, DNA methylation is lost passively through successive cell divisions (Figure 2)[33].

Some studies[34,35] have shown that 5hmC is present in different normal human tissues. However, 5hmC levels and expression of TET enzymes are down-regulated in various human cancers[36-38], including gynecological cancers, such as cervical, endometrial, and ovarian.

Cervical Cancer

Cervical cancer (CC) ranks as the second most common gynecological cancer in incidence and mortality, with 604,127 new cases and 341,831 new deaths estimated in 2020 worldwide[39]. A total of 14,100 new cases and 4,280 new deaths were estimated in the United States in 2022[40]. According to the Human Development Index (HDI), CC ranks second in incidence and mortality in

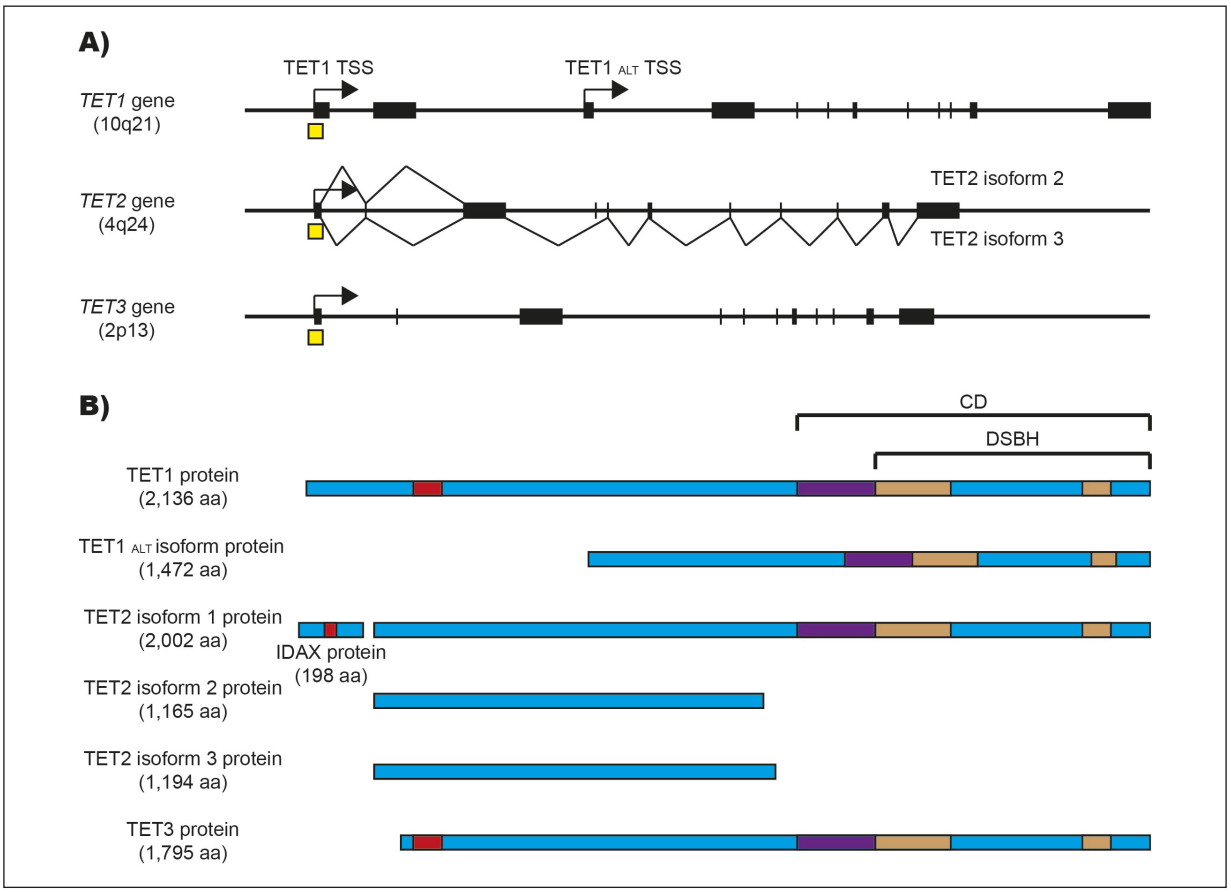

Figure 1. Structure of TET1, TET2, and TET3. **A**, The structure of the TET1 (upper), TET2 (middle), and TET3 (lower) genes are shown. Black box: exon. Yellow box: CpG island. **B**, Structure of TET proteins. The structure of TET1 (upper), TET2 (middle), and TET3 (lower) proteins is shown. Red box: CXXC domain. Purple box: Cys-rich region. Brown box: domain of interaction with Fe(II) (left) and 2-OG (right). CD: Catalytic domain. DSBH: Double Stranded Beta Helix domain.

countries with HDI lower[39]. It is well known that the main risk factors are infection by High Risk-HPV (HR-HPV), immunosuppression by HIV, smoking, a high number of full-term pregnancies, long-term use of oral contraceptives, multiple sexual partners, and first sexual intercourse at a young age[41-43]. Moreover, there are key epigenetic factors in cervical carcinogenesis, including DNA methylation, which is a well-characterized epigenetic modification in CC[44], while the role of TET proteins and 5hmC remains largely unknown.

TET1 expression is decreased in CC tissue samples compared with non-cancerous cervical tissue samples and correlates with advanced FIGO stage, advanced grade of differentiation, and squamous histological type[45]. Interestingly, in cervical precancerous lesion tissue samples, the TET1 expression is increased compared to squamous epithelium without lesion tissue samples[46]. TET2 expression is decreased in CC tissue compared with matched non-tumor tissue samples and correlates with poor Overall Survival (OS) and Disease-Free Survival (DFS), advanced FIGO stage, advanced tumor grade, lymph node metastasis, vascular invasion, and low 5hmC levels[47]. In addition, TET2 expression negatively correlates with the methylation level in its promoter and positively correlates with immune-infiltrating tumor-associated fibroblasts and immunization routes, such as activated B and CD4 T cells in patients with CC[48]. The 5hmC levels decrease in CC and correlate with poor OS and DFS[47,49].

Some frameshift mutations in the *TET1* gene were identified in recurrent tumors after radiotherapy compared with a treatment-naive tumor in CC, suggesting that alterations in the *TET1* gene could be involved in radioresistance[50]. In addition, the mutation (R1516*/Q) was identified in the TET2 protein in a patient with CC[48].

Little is known about the molecular mechanism involved in TET1 deregulation in CC. The aberrant methylation in the *TET1* promoter negatively

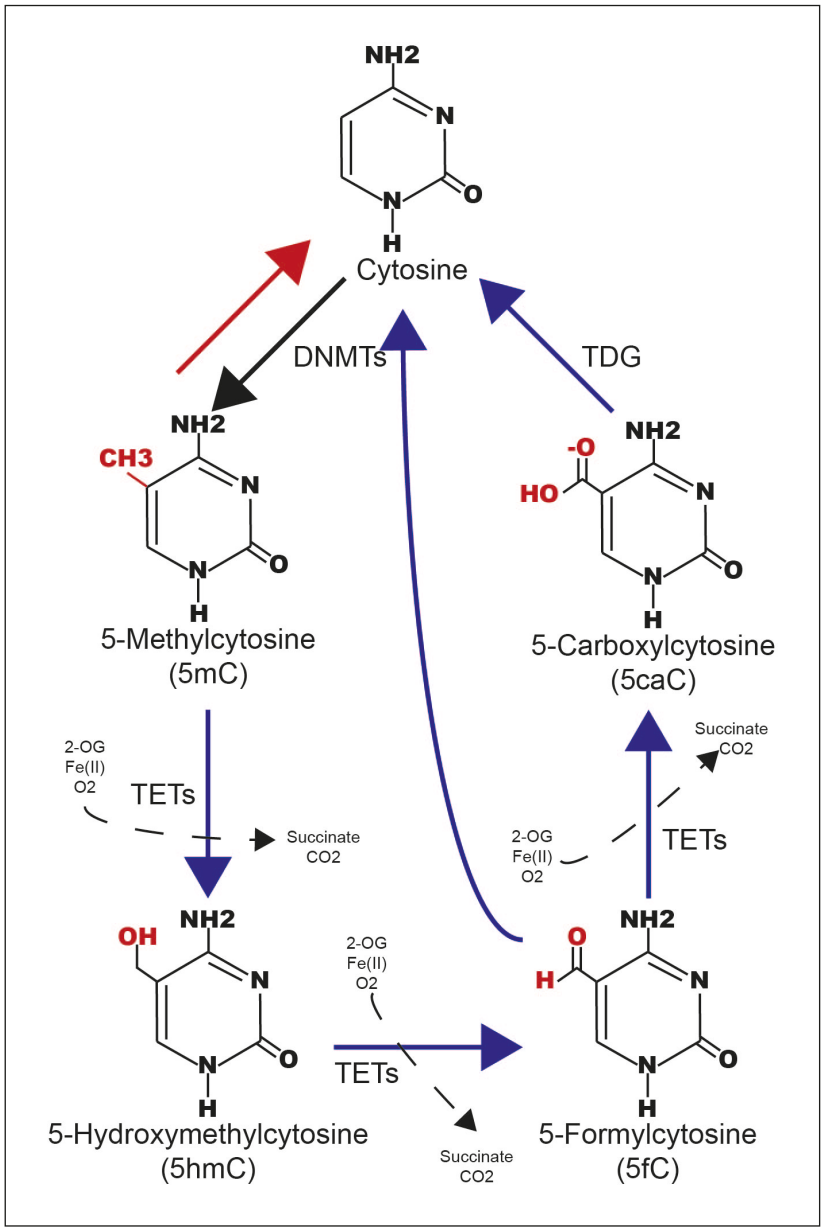

Figure 2. Mechanism of DNA demethylation by TET enzymes. Black arrow: DNA methylation. Red arrow: Passive demethylation. Blue arrow: Active demethylation. Black arrow with the dashed line: Indicate the substrate and products of oxidation.

correlates with its expression in CaSki, HeLa, and SiHa CC cells, but not C-33A CC cells[51]. On the other hand, the long noncoding RNA (lncRNA) HOTAIR indirectly inhibits TET1 expression *via* methylation of its promoter in HeLa cells, and TET1 re-expression decreases the Wnt/β-catenin signaling pathway by demethylation in promoters of negative regulators of this signaling pathway[52]. Moreover, Snail/PRMT5/NuRD complex inhibits the TET1 expression; this increases the 5mC levels and decreases the 5hmC levels *in vivo* and *in vitro*[53]. Interestingly, TET1 promotes stemness through an increase in SOX2 and NESTIN expression *via* 5hmC, and inhibits Epithelial-Mesenchymal Transition (EMT), decreasing ZEB1 and VIMENTIN expression through its interaction with LSD1 and EZH2 in Z172 and Z183 precancerous cervical cells, avoiding the malignant transformation of HPV-immortalized cells[46].

Several studies have reported the use of CD of TET enzymes to induce the expression of TSG *via* demethylation of their promoters in CC. In this sense, TET1CD-dCas9 fusion protein increases 5hmC levels and promotes site-specific demethylation in the *BRCA1* gene promoter, increasing its expression and inhibiting the cell proliferation of HeLa cells[54]. Another TET1CD-dCas9 fusion protein promotes the demethylation in the

Eph7A gene promoter and increases its expression in SiHa and Ca Ski cells[55]. An artificial transcription factor fused to the TET2 CD in combination with Trichostatin A (TSA) treatment increases EPB41L3 expression in Ca Ski CC cells[56]. Similarly, an artificial transcription factor fused to the TET2 CD increases TFPI2 and C13ORF18 expression by demethylation of their promoters, which decreases the cell proliferation, viability, and colony formation and increases apoptosis in CC-11, Ca Ski, and HeLa CC cells[57].

Endometrial Cancer

Endometrial cancer (EC) is the third gynecological cancer most frequent worldwide, with an estimated 417,367 new cases and 97,370 new deaths in 2020[39]. Its incidence is increasing in countries with very high HDI, such as the United States, where the EC ranks as the second most common cancer among women, with an estimated 65,950 new cases and 12,550 new deaths in 2022[40]. The main risk factors are obesity, resistance to insulin, advancing age, early menarche, late menopause, chronic anovulation, nulliparity, and menopausal hormonal use[58-60]. The role of DNA methylation in EC61 is well known; however, the role of TET enzymes and 5hmC has not been well characterized.

TET1 and TET2 expressions are decreased, and TET3 expressions are increased in EC tissue samples compared with normal endometrial tissue samples. TET1 and TET2 expressions are lower in advanced FIGO stages, advanced histological differentiation grade, and lymph node metastasis[62,63]; in contrast, TET3 expression is higher in these groups. TET1 and TET2 expression positively correlates with 5hmC levels; however, only low TET1 expression correlates with shorter OS[62,64]. In contrast, the expression of the $TET1^{ALT}$ isoform is increased in EC tissue samples compared with normal endometrial tissue and correlates with shorter OS in patients with EC[24]. TET2 expression positively correlates with immunization routes, including routes as activated CD8 T and dendritic cells, and some neoantigens, while it negatively correlates with tumor mutational burden and the tumor microenvironment in patients with EC. Moreover, the methylation in the *TET2* gene is increased and correlates with poor OS[48]. Finally, 5hmC levels are downregulated in patients with EC and correlate with clinical stage, differentiation, depth of myometrial invasion, lymph node metastasis, and OS[63].

Some Single Nucleotide Polymorphisms (SNPs) and mutations in TET2 have been identified, such as rs7679673, which is located ~6 kb upstream of *TET2* gene and C allele is associated with the risk of EC in women of European ancestry[65]. Another SNP is the rs6839705 SNP, localized in an intron of the *TET2* gene, and the C allele is associated with the risk of EC in European and American women[66]. A missense mutation was identified in the *TET2* gene in the Taiwanese population with EC. The mutation is C>T, localized to 3,116 nucleotides from the *TET2* encoding gene and induces a change of Ser1039Leu in the TET2 protein[67]. Recently, it was reported that the phosphorylation in S38 of TET2 protein is more increased in patients with EC (particularly in grade 2) than in non-tumoral tissue samples. Other genetic alterations, such as missense mutations (most commonly R1516*/Q) in the *TET2* gene were identified in 9.07% of patients with EC. These genetic alterations were associated with a good OS, Progression-Free Survival (PFS), and Disease-Specific Survival (DSS) in female cancers, including EC[48].

MiR-191 binds to TET1 mRNA 3′-UTR and decreases its expression; however, TET1 re-expression increases APC expression *via* demethylation of its promoter, inhibiting cell viability of Ishikawa and HEC-1A EC cells[68]. TET3 induces the expression of maker genes of EMT, such as TWIST1 and ZEB1, through the binding to chromatin and histone modifications (H3K4me3, H2BK120Ub, and H2B S112GlcNAc) in HEC-1A and Ishikawa EC cells[69].

Studies[63-74] have suggested that TET enzymes could be potential therapeutic targets in EC; IDH1 increases TET1 expression, which induces Nrf2 expression *via* demethylation of its promoter in Ishikawa and Spec2 EC cells. Nrf2 induces cisplatin and paclitaxel resistance and cell growth. Metformin treatment decreases IDH1, TET1, and Nrf2 expression and promotes cisplatin and paclitaxel sensitivity[70]. Metformin increases *via* AMPK the TET2 expression and 5hmC levels in Ishikawa and HEC-1A EC cells, decreasing cell proliferation[63]. Progestin is another chemotherapeutic drug used in EC therapy, and TET sensitizes the EC cells to this treatment. Mechanistically, NrCAM increases the TET1 expression, which induces the PR expression *via* hydroxymethylation of the promoter of the *PRB* gene in Ishikawa and ECC-1 EC cells[71]. Unfortunately, EC patients need high doses of progestin for a long time, inducing resistance. Therefore, TET1 induces GLO1 expression *via* demethylation of its promoter, which is involved in resistance to progestin in

Ishikawa and ECC-1 EC cells[72]. Similarly, TET1 and TET2 promote a Cancer Stem Cell (CSC) state by increasing the NANOG, SOX2, and OCT4 expression *via* hydroxymethylation of their promote, promoting the resistance to progestin treatment in EC cells. However, embryonic microenvironment-derived ALPP suppresses TET1 and TET2 expression, promoting the differentiation of CSC EC cells and reducing the resistance to progestin treatment[73]. Finally, Progesterone and E2 treatment decrease TET1 expression in AN3 EC cells. However, TET1 and TET3 expression is increased in RL95-2 EC cells[74].

Insulin resistance is a risk factor for EC[58], and interestingly, the TET1 expression is increased in EC tissue samples with insulin resistance compared with EC tissue samples without insulin resistance[75]. Insulin increases TET1 expression, which induces the GPER expression, activates the PI3K/AKT/Cycling D1 signaling pathway, and promotes cell proliferation in Ishikawa and HEC-1A EC cells[76]. Mechanistically, insulin induces TET1 expression through PI3K/AKT signaling pathway. TET1 induces GPER expression by increasing the 5hmC levels of its promoter in Ishikawa and HEC-1A EC cells[75]. Insulin resistance promotes inflammation, and chronic inflammation induces macrophage (CD68+ CD163+) infiltration, promoting EC cell proliferation. Macrophages produce inflammatory cytokines, including IL17A; these cytokines bind to IL17R to induce TET1 expression. TET1 induces ERα expression through an increase in 5hmC levels of its promoter. Lastly, ERα activates PI3K/AKT signaling pathway in HEC-1A EC cells[77].

Ovarian Cancer

Ovarian cancer (OC) is the fourth most common gynecological cancer in incidence and mortality worldwide, with an estimated 313,959 new cases and 207,252 new deaths in 2022[39]. In the United States, there were an estimated 19,880 new cases and 12,810 new deaths in 2022[40]. The main risk factors are family history, obesity, smoking, endometriosis, hormone replacement therapy use, nulliparity, and mutations in *BRCA1* and *BRCA2* TSG[78-80]. Some studies[81-83] have reported the role of DNA methylation in OC; nevertheless, the underlying molecular mechanism of TET enzymes and 5hmC are largely unknown.

TET1 expression is decreased in several OC cells, and OC tissue samples compared with normal ovary tissue samples and correlates with advanced stages in patients with serous OC and OS[51,84,85]. In contrast, the expression of the TET1^{ALT} isoform is increased in OC tissue samples and correlates with poor OS[24]. Conversely, TET1 expression is increased in epithelial OC tissue samples, as well as in CSC obtained from OC cells (A2780, HeyC2, ES2, SKOV3, and CP70) and patients compared with benign tumor tissue samples and correlates with 5hmC levels and poor PFS. According to EC subtypes, TET1 expression is increased in papillary serous ovarian adenocarcinoma, serous tubal intraepithelial carcinomas, and HGSOC tissue samples compared with normal ovarian and normal oviduct surface epithelium brushing samples. Interestingly, TET1 expression increases sequentially from normal fallopian tubal epithelium to invasive high-grade serous ovarian cancer in OC patients[86].

The TET2 expression is decreased in epithelial OC tissue samples and SKOV-3, COC1, A2780, and ES-2 OV cells, compared with normal ovarian tissue samples and HOSEpiC cells. Low TET2 expression correlates with advanced stages, advanced differentiation grade, metastatic lymph node, vascular thrombosis, poor OS, and poor PFS in epithelial OC patients, particularly in endometroid subtype, grade 1-2, debulk optimal, and stages 1-2[48,87,88]. Interestingly, some parameters, such as a poor OS, PFS, and the presence of mutated p53 were associated with a high TET2 expression in patients with OC. Moreover, the TET2 promoter is methylated and negatively correlates with its expression in OC patients. TET2 expression positively correlates with immune infiltrating-tumor-associated fibroblasts[48].

TET3 expression is decreased in OC tissue samples compared with normal ovarian tissue samples, particularly in serous histopathological subtype; it is associated with an advanced differentiation grade and decreases according to the clinical stages and pathological grades[89,90]. Conversely, a bioinformatic study showed that TET3 expression is increased in OC tissue samples compared to normal ovarian tissue samples, particularly in endometrioid adenocarcinoma and clear cell adenocarcinoma tissue samples compared with normal ovarian tissue samples. Similarly, TET3 expression is higher in borderline tumors and advanced stage in serous OC tissue samples, and it correlates with poor OS in OC, serous type, high grade, and advanced stages in OC patients[91].

The 5hmC levels are decreased in epithelial primary and metastatic OC tissue samples, as

well as ES-2 and HO8910 OC cells compared with non-tumoral ovarian tissue samples. Low 5hmC levels correlate with advanced stages, advanced differentiation grade, metastatic lymph node, vascular thrombosis, and poor OS in OC patients[84,87]. The 5hmC levels are decreased in patients with cisplatin resistance compared with patients who responded to cisplatin therapy, and low 5hmC levels correlate with poor OS and PFS following cisplatin-based chemotherapy[92].

Several mutations have been identified in *TET* genes or proteins in OC patients, including the non-synonymous[93-96]. Single Nucleotide Variant (SNV) in exon 2 of the TET1 gene (c.C767T:p.A256V) was identified in a OC patient with alterations in *BRCA* phenocopies[93]. On the other hand, several mutations with changes in amino acids (PHGVS), such as the p.Ser473delinsTerAla, p.Tyr1679fs, p.Val1426fs, p.His1380Tyr, p.Cys1378Arg, p.Gln876*, p.Ser1246Leu, p.Gln769fs, p.Gln273*, p.Glu283fs, p.Ala1283Pro, and p.Lys1197Glu were identified in *TET2* gene in OC patients[94]. A copy number loss in the *TET2* gene was found in Korean patients with ovarian clear cell carcinoma subtype[95]. The rs6839705 SNP is located in an intron of the *TET2* gene and is associated with the risk of OC in European and American women[66]. A frameshift deletion located in the *TET2* gene (p.C1281Vfs*82) was reported in patients with OC adult-type granulosa cell tumor[96]. Finally, the nonsynonymous SNV in exon 3 of the *TET2* gene (c.C86G:p.P29R) was identified in a patient with a tumor of *BRCA* phenocopies[93].

Studies[84-92] have reported the molecular mechanism of TET proteins in OC. TET1 increases 5hmC levels, decreases cell proliferation in ES-2 OC and A2780 cells, suppresses tumor growth, and promotes apoptosis *in vivo*. TET1 induces RASSF5 expression *via* demethylation of its promoter, which decreases cell proliferation in A2780 OC cells[84]. TET1 elevates the 5hmC level and decreases methylation level in the promoters of the *SFRP2* and *DKK1* genes, inducing their expression. SFRP2 and DKK1 are the two main upstream antagonists of the Wnt/β-catenin signaling pathway. Thus, SFRP2 and DKK1 decrease cell migration, proliferation, invasion, EMT, and metastasis in SKOV3 and OVCAR3 OC cells[85]. Conversely, TET1 promotes cell migration, proliferation, and chemoresistance, particularly to cisplatin and taxol, in A2780, HeyC2, and SKOV3 OC cells, as well as tumor growth *in vivo*, through the re-expression of Yamanaka factors and CSC marker genes (*ALDH1, CD117, CD133, CD44, LGR5, NANOG, NES, OCT4, SOX2, KLF4,* and *c-Myc* genes) in A2780, HeyC2, and SKOV3 OC cells. Moreover, TET1 increases the expression of genes involved in oncogenic signaling pathways, such as RAS/RAF, ERBB2, VEGF, TGF-β, and EGFR in SKOV3 and HeyC2 OC cells, and induces the expression of the *CK2α* gene through the increase of 5hmC levels in its promoter in SKOV3 and HeyC2 OC cells, which increases tumor growth *in vivo*[86]. TET1 induces Vimentin expression through the demethylation of its promoter to promote cisplatin resistance, migration, invasion, and EMT and decreases apoptosis in A2780 and CP70 OC cells[97]. GATA6-AS1 represses the miR-19a-5p expression, increasing the TET2 expression, which decreases cell proliferation and migration in ES-2 and SKOV-3 OV cells[88]. On the other hand, TGF-β1 decreases TET3 expression but no TET1 or TET2 expression. TET3 induces miR-30d expression *via* demethylation, inhibiting the EMT in SKOV3 and 3AO OC cells[89]. Interestingly, expression of TET proteins is increased in cisplatin resistance CP70, OVCAR3, SKOV3, and MPSC1 OC cells compared with parent cells[86,97]. In this sense, 5-aza increases the expression of TET proteins in cisplatin-resistant A2780 OC cells, OVCAR4, CaOV3, and OVSAHO HGSOC OC cells. Finally, TET2 over-expression increases 5hmC levels and decreases the cell subpopulation associated to CSC, specifically the cell side population, and sensitive the cells to cisplatin in cisplatin-resistant A2780 OC cells[92].

Berberine is an alkaloid extracted from Coptis and Phellodendron plants and inhibits the Warburg effect in SKOV3 and 3AO OV cells. Mechanistically, berberine increases TET3 expression, which demethylates the promoter of miR-145, inducing its expression. MiR-145 down-regulates the expression of key genes involved in the Warburg effect, such as the *HK2* gene[90].

Future Perspectives

Studies[45-49,62-65,84-94] have reported alterations in the expression of TET1, TET2, and TET3 enzymes, as well as 5hmC levels, in gynecological cancers; however, there is still much to investigate. Therefore, future studies are needed to elucidate the molecular mechanisms involved in the deregulation of TET enzymes and 5hmC levels that involved long noncoding RNAs and circular RNAs, as well as the molecular mechanisms downstream in these types of human cancers.

On the other hand, it is important to analyze the expression of TET proteins as potential diagnostic, prognostic, and therapeutic biomarkers in serum or plasma samples of patients with CC, EC, and OC, as a non-invasive method, as well as to evaluate their sensitive and specificity of each one or in combination with the used biomarkers.

Conclusions

In summary, the expression of TET1, TET2, and TET3 enzymes is deregulated in cervical, endometrial, and ovarian human cancers by several molecular mechanisms that involve miRNAs and transcription factors. Deregulation of TET enzymes alters the 5hmC levels in these cancers. TET enzymes and 5hmC play a critical role in carcinogenesis, progression, and response to gynecological cancers through their catalytic activity, promoting the DNA demethylation on promoters of TSG.

Authors' Contributions

Conceptualization, E.G.S.B. and A. E. Z. G..; formal analysis, P. A. A. L., M. A. M. C. and J. O. O.; investigation, H. J. W., J. O. O. and V. A. V.; writing—original draft preparation, C. J. B. H., A. E. Z. G., M. A. M. C. and E.G.S.B.; writing—review and editing, P. A. A. L., E.G.S.B. and V. A. V. All authors have read and agreed to the published version of the manuscript. All authors read and approved the submitted final version.

Conflict of Interests

The authors declare no conflict of interest.

Ethics Approval

Not applicable.

Informed Consent

Not applicable.

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