



Review

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LG-ESSs and HG-ESSs: underlying molecular alterations and potential therapeutic strategies

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Abstract: Endometrial stromal tumors (ESTs) include endometrial stromal nodule (ESN), low-grade endometrial stromal sarcoma (LG-ESS), high-grade endometrial stromal sarcoma (HG-ESS), and undifferentiated uterine sarcoma (UUS). Since these are rare tumor types, there is an unmet clinical need for the systematic therapy of advanced LG-ESS or HG-ESS. Cytogenetic and molecular advances in ESTs have shown that multiple recurrent gene fusions are present in a large proportion of LG-ESSs, and HG-ESSs are identified by the tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein epsilon (*YWHAE*)-family with sequence similarity 22 (*FAM22*) fusion. Recently, a group of ESSs harboring both zinc finger CCCH domain-containing protein 7B (*ZC3H7B*)-B-cell lymphoma 6 corepressor (*BCOR*) fusion and internal tandem duplication (ITD) of the *BCOR* gene have been provisionally classified as HG-ESSs. In this review, we firstly describe current knowledge about the molecular characteristics of recurrent aberrant proteins and their roles in the tumorigenesis of LG-ESSs and HG-ESSs. Next, we summarize the possibly shared signal pathways in the tumorigenesis of LG-ESSs and HG-ESSs, and list potentially actionable targets. Finally, based on the above discussion, we propose a few promising therapeutic strategies for LG-ESSs and HG-ESSs with recurrent gene alterations.

Key words: Low-grade endometrial stromal sarcoma (LG-ESS); High-grade endometrial stromal sarcoma (HG-ESS); Molecular genetics; Therapeutics

1 Introduction

Endometrial stromal tumors (ESTs) are rare types of mesenchymal tumors. In 2014, four categories of ESTs were recognized by the World Health Organization (WHO), including endometrial stromal nodule (ESN), low-grade endometrial stromal sarcoma (LG-ESS), high-grade endometrial stromal sarcoma (HG-ESS), and undifferentiated uterine sarcoma (UUS) (Conklin and Longacre, 2014). Among these, LG-ESSs are relatively indolent tumors characterized by multiple or late relapses. The prognosis of HG-ESSs harboring tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein epsilon (*YWHAE*)-NUT midline carcinoma family member 2 (*NUTM2*) fusion protein is worse than that of LG-ESSs but better than that of UUS; the latter is typically associated with poor outcomes.

Surgery is the principal primary therapy for LG-ESS, HG-ESS, and UUS, which are relatively radio- and chemoresistant (Conklin and Longacre, 2014; Seagle et al., 2017; Ferreira et al., 2018; Thiel and Halmen, 2018). Effective systemic therapy for metastatic LG-ESS, HG-ESS, and UUS is therefore urgently required. A growing body of research on chromosomes and cytogenetics has shown some recurrent genetic aberrations in LG-ESSs and HG-ESSs. These genetic alterations are undoubtedly beneficial for establishing novel effective systemic therapies for ESSs. Accordingly, this review addresses the known molecular alterations and recent potential developments for the treatment of LG-ESS and HG-ESS.

2 Molecular alterations in LG-ESSs and HG-ESSs

2.1 Recurrent fusion genes in LG-ESSs

2.1.1 *JAZF1-SUZ12*

The most frequent genetic aberration in LG-ESSs is the t(7;17)(p15;q21) chromosomal translocation

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(Sreekantaiah et al., 1991; Hennig et al., 1997), resulting in the juxtaposed with another zinc finger gene 1 (*JAZF1*)-suppressor of zeste 12 (*SUZ12*) (formerly named *JAZF1-JJAZ1*) fusion gene that is present in approximately 50% of LG-ESS cases (Table 1) (Hrzenjak, 2016). The putative *JAZF1-SUZ12* fusion protein contains an N-proximal zinc finger domain from *JAZF1*, a zinc finger domain and a VEFS-box (VRN2-EMF2-FIS2-*SUZ12* box) domain in the C-terminal from *SUZ12* (Ma et al., 2017).

Multiple studies have shown that *JAZF1* expression is involved in the tumorigenesis of prostate, gastric, and hepatocellular carcinomas (Ueyama et al., 2016; Sung et al., 2018; Mei et al., 2019). Most recently, the *JAZF1* protein was identified as a new subunit of the nucleosome acetyltransferase of H4 (NuA4) complex (Piunti et al., 2019). *SUZ12* is one of the core components of polycomb repressive complex 2 (PRC2) required for the minimum histone methyltransferase (HMT) activity and is involved in the formation of middle lobe and docking lobe of PRC2 for stabilizing the active sites and recruiting the factors associated with PRC2 (Chen et al., 2018; Chammas et al., 2020).

As a dynamic and active participant in multiple nuclear processes, chromatin regulates gene expression in eukaryotic cells. The chromatin structure is continuously modified to fulfil its actual role. The key regulators of chromatin structure for gene expression are histone methylation complexes of which PRC2 is the major class with HMT activity (Birve et al.,

2001). PRC2 and its components, which control chromatin compaction and transcription repression through trimethylated lysine 27 on histone 3 (H3K27me3), have been recently associated with carcinogenesis and metastasis (Studach et al., 2012; Lee W et al., 2014; Prieto-Granada et al., 2016; Oppel et al., 2020). Histone acetyltransferase (HAT) complexes are also key regulators of chromatin structure for gene expression. For example, the NuA4 HAT complex carries out a significant proportion of all nuclear acetylation and is critical for transcriptional regulation, functioning as a co-activator of key cellular proteins, such as nuclear hormone receptors, β -catenin, nuclear factor- κ B (NF- κ B), and c-Myc oncoprotein. Thus, NuA4 HAT complex has been unsurprisingly linked to oncogenesis (Avvakumov and Côté, 2007).

The *JAZF1-SUZ12* fusion protein was found to retain the ability to interact with both NuA4 and PRC2, acting as a molecular bridge between the two complexes (Piunti et al., 2019). It destabilizes PRC2 components, namely enhancer of zeste homolog 2 (EZH2) and embryonic ectoderm development (EED), prevents the co-localization of *SUZ12* with EZH2 and EED, abolishes the HMT activity of the PRC2 complex, and decreases the level of H3K27me3 (Ma et al., 2017). Meanwhile, the same study showed that PRC2 containing the *JAZF1-SUZ12* fusion protein has decreased binding affinity to target chromatin loci, and thus the repression of target genes is reduced, leading to inhibited normal differentiation of endometrial

Table 1 Recurrent cytogenetic and molecular alterations and possible pathogenic mechanism of ESSs

Subtype of ESS	Cytogenetic alteration	Molecular alteration	Possible pathogenic mechanism
LG-ESS	t(7;17)(p15;q21)	<i>JAZF1-SUZ12</i>	Decreased HMT activity
	t(6;7)(p21;p22)/t(6;7)(p21;p15)	<i>JAZF1-PHF1</i>	Decreased HMT activity
	t(6p;10q;10p)	<i>EPC1-PHF1</i>	Decreased HMT activity and inappropriate HAT activity
	ins(6;2)(p21;q23q23)	<i>EPC2-PHF1</i>	Decreased HMT activity
	t(1;6)(p34;p21)	<i>MEAF6-PHF1</i>	Decreased HMT activity and inappropriate HAT activity
		<i>MBTD1-PHF1</i>	Decreased HMT activity
	t(5;6)(q31;p21)	<i>BRD8-PHF1</i>	Decreased HMT activity and altered HAT activity
	t(X;17)(p11;q21)	<i>MBTD1-CXorf67</i>	Decreased HMT activity
HG-ESS	t(10;17)(q22;p13)	<i>YWHAE-NUTM2</i>	Affected PI3K-AKT and MAPK pathways
	t(X;22)(p11;q13)	<i>ZC3H7B-BCOR</i>	Affected epigenetic regulation
	<i>BCOR</i> ITD	<i>BCOR</i> ITD	Hindered binding of PRC2 via PRC1.1

ESS: endometrial stromal sarcoma; LG-ESS: low-grade endometrial stromal sarcoma; HG-ESS: high-grade endometrial stromal sarcoma; *BOCR*: B-cell lymphoma 6 corepressor; ITD: internal tandem duplication; *JAZF1*: juxtaposed with another zinc finger gene 1; *SUZ12*: suppressor of zeste 12; PHF: plant homeodomain finger protein; EPC: enhancer of polycomb homolog; MEAF6: MYST/Esa1-associated factor 6; MBTD1: malignant brain tumor domain-containing protein 1; BRD8: bromodomain-containing protein 8; CXorf67: chromosome X open reading frame 67; YWHAE: tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein epsilon; NUTM2: NUT family member 2; ZC3H7B: zinc finger CCCH domain-containing protein 7B; HMT: histone methyltransferase; HAT: histone acetyltransferase; PI3K: phosphatidylinositol-3-kinase; AKT: serine/threonine kinase; MAPK: mitogen-activated protein kinase; PRC: polycomb repressive complex.

stromal cells and increased cell proliferation (Ma et al., 2017). Another study by Li et al. (2007) further demonstrated that the JAZF1-SUZ12 fusion protein causes allelic exclusion and in turn the suppression of unrearranged SUZ12 allele, leading to markedly inhibited apoptosis and accelerated cellular proliferation.

All findings support that the JAZF1-SUZ12 fusion protein is involved in the pathogenesis of LG-ESS at least through altering PRC2 function (Table 1). To our knowledge, no study has explored whether and how the JAZF1-SUZ12 fusion protein functionally alters the NuA4 complex with JAZF1-SUZ12 retaining the ability to interact with NuA4.

2.1.2 *PHF1*-targeting fusions

The second most frequent genetic aberration in LG-ESSs involves chromosomal band 6p21, in which the plant homeodomain (PHD) finger protein 1 (*PHF1*) gene is located. The PHF1 protein is an essential factor for epigenetic regulation and genome maintenance, and contains two kinds of histone reader modules, namely one Tudor domain and two PHD zinc finger domains, as well as an extended homology domain (Chammas et al., 2020). Crystallographic and functional studies revealed that PHF1, as a PRC2 accessory protein, binds DNA by its winged helix (WH) domain that is formed by the conserved region located C-terminally to the second PHD finger domain (PHD2) of PHF1. This binding of PHF1-DNA accounts for the extended residence time of PRC2 on chromatin (Choi et al., 2017) and is the reason why PHF1 more efficiently promotes EZH2, a catalytic component of PRC2, to catalyze H3K27 trimethylation, and that a reduced level of PHF1 leads to a decreased global level of H3K27me3 (Sarma et al., 2008; Choi et al., 2017). Based on the above relationship, PHF1 is functionally important for H3K27 trimethylation.

Besides PRC2, one study revealed several other PHF1-interacting epigenetic factors and complexes, such as the protein arginine methyltransferase 5 (PRMT5)-WD repeat domain 77 (WDR77) complex, Cullin4B-Ring E3 ligase complex (CRL4B), SIN3 transcription regulator family member A/histone deacetylase (SIN3A/HDAC) complex, nucleosome remodeling deacetylase (NuRD) complex, and amplified in breast cancer 1 (AIB1), indicating that PHF1 participates in various epigenetic transcriptional regulation pathways (Liu et al., 2018).

To date, multiple studies have shown that *PHF1* recombines with multiple fusion partners, including the *JAZF1* gene from 7q21, enhancer of polycomb homolog 1 (*EPC1*) gene from 10p11, *EPC2* gene from 2q23, MYST/Esa1-associated factor 6 (*MEAF6*) gene from 1p34, bromodomain-containing protein 8 (*BRD8*) gene from 5q31, and malignant brain tumor (MBT) domain-containing protein 1 (*MBTD1*) gene from 17q21. The protein products of these fusion genes are all components of the NuA4 complex (Micci et al., 2006, 2014, 2017; Panagopoulos et al., 2008, 2012; Chiang et al., 2011; Brunetti et al., 2018; Makise et al., 2019; Han et al., 2020). All of the PHF1 fragments in these chimeric proteins, including JAZF1-PHF1, EPC1-PHF1, EPC2-PHF1, MEAF6-PHF1, MBTD1-PHF1, and BRD8-PHF1, contain the WH domain that is important for H3K27 trimethylation. It is reasonable to speculate that the conformation of these chimeric proteins might hinder the engagement between PHF1 and DNA by the WH domain, leading to a shortened residence time of PRC2 on chromatin, reduced level of HMT activity, and released repression of target genes. This might be the common pathogenic pathway for all LG-ESSs with PHF1-related fusion proteins (Table 1).

2.1.2.1 *JAZF1-PHF1*

Unbalanced t(6p;7p) leads to the formation of fusion gene *JAZF1-PHF1*. Although chimeric transcripts of *JAZF1-PHF1* are varied, all putative JAZF1-PHF1 proteins retain one zinc finger domain from the *JAZF1* gene and all functional domains from the *PHF1* gene (Table 1) (Micci et al., 2006; Panagopoulos et al., 2008).

Considering the above speculated common pathogenic mechanism of PHF1-related fusion proteins, little is currently known about how the JAZF1-PHF1 fusion protein disturbs the functions of PRC2 and NuA4; therefore, additional studies are needed to identify how the JAZF1-PHF1 fusion is involved in the pathogenesis of LG-ESS.

2.1.2.2 *EPC1-PHF1* and *EPC2-PHF1*

The *PHF1* gene is recombined with *EPC1* gene from 10p11 through unbalanced 6p;10p rearrangements (Micci et al., 2006) and the *EPC2* gene through ins(6;2)(p21;q23q23) (Table 1) (Brunetti et al., 2018). The EPC1-PHF1 fusion protein contains the first 581 residues from EPC1 and the entire coding region of *PHF1* (Micci et al., 2006). The fusion of *EPC2-PHF1* retains the entire coding regions from both genes, and the putative protein consists of 855 amino acid

residues from EPC2 and 662 amino acids from PHF1 (Brunetti et al., 2018). *EPC1* and *EPC2* are two splice variants of *EPC*. Multiple studies have focused on either *EPC1* or *EPC2* independently, yet it generally remains unclear under what conditions one paralog may be preferentially critical (Stankunas et al., 1998).

Both *EPC1*-PHF1 and *EPC2*-PHF1 might share the above speculated common pathogenic mechanism of PHF1-related fusion proteins, namely disturbing the HMT function of PRC2 by hindering the engagement between PHF1 and DNA. Additionally, some researchers proposed that the *EPC1*-PHF1 fusion protein is involved in the tumorigenesis of LG-ESS by the inappropriate HAT activity to PHF1's normal targets (Table 1). The details of this mechanism are discussed below.

Conserved from yeast to human, the subunits of the NuA4 complex are organized into distinct functional modules. Piccolo module, including Tat interacting protein 60 (TIP60; Esa1 in yeast), *EPC1* (Epl1 in yeast), inhibitor of growth family member 3 (ING3; YNG2 in yeast), and MEAF6 (Eaf6 in yeast), is one of the functional modules of the NuA4 complex and is capable of acetylating chromatin substrates (Boudreault et al., 2003). Within NuA4, the N terminus of *EPC1* binds TIP60, ING3, and MEAF6, whereas the C terminus bridges *EPC1* and the rest of the NuA4 complex via MBTD1 (Avvakumov and Côté, 2007; Zhang et al., 2020). However, the study has shown that the *EPC1* residues 644–672, which are associated with the binding of *EPC1* with MBTD1, are not included in the *EPC1*-PHF1 fusion protein (Zhang et al., 2020). Thus, the *EPC1*-PHF1 fusion protein cannot bridge the Piccolo-NuA4 and the rest of the NuA4 complex, resulting in the lack of intact NuA4 complex formed. Boudreault et al. (2003) showed that cells expressing only the N-terminal half of Epl1 lack intact NuA4 HAT activity but possess Piccolo-NuA4 complex and subsequent activity. It was further proposed that Piccolo-NuA4 represents a nontargeted HAT activity responsible for global acetylation, whereas the intact NuA4 complex is recruited to specific genomic loci to locally perturb the dynamic acetylation/deacetylation equilibrium. Based on the above findings, Avvakumov and Côté (2007) proposed a highly intriguing possibility that the *EPC1*-PHF1 chimeric protein diverts the HAT activity of Piccolo-NuA4 to PHF1's normal targets—genomic regions normally maintained in a repressed state. The mistargeted acetylation of histone H4 by

Piccolo-NuA4 would lead to the unravelling of heterochromatin, resulting in aberrant gene expression that could easily account for the appearance of malignancy.

2.1.2.3 *MEAF6-PHF1*

The *MEAF6-PHF1* fusion gene originates from t(1;6)(p34;p21) (Table 1). The transcript is an in-frame fusion between exon 5 of *MEAF6* and exon 2 of *PHF1*, and the predicted fusion protein contains the Tudor domain and tandem PHD zinc finger domains of PHF1 and the NuA4 subunit MEAF6 (Panagopoulos et al., 2012; Micci et al., 2014).

In the Piccolo-NuA4, MEAF6 is an accessory factor that physically interacts with the *EPC1* and TIP60 under normal circumstances (Avvakumov and Côté, 2007). Until now, the specific role of MEAF6 has not been elucidated, while, as a noncatalytic subunit, it is known to be critical for the assembly, stability, genomic targeting, substrate specificity, and regulation of the NuA4 complex. Furthermore, the role of MEAF6-PHF1 fusion in the tumorigenesis of LG-ESS is also unclear. Panagopoulos et al. (2012) assumed a mechanism similar to the *EPC1*-PHF1, namely the MEAF6-PHF1 chimeric protein bridging Piccolo-NuA4 with PRC2 and diverting Piccolo-NuA4 activity toward PHF1's normal genomic targets. In the same way, the above speculated common pathogenic mechanism of PHF1-related fusion proteins, namely disturbed HMT function of PRC2 complex, also applies to MEAF6-PHF1.

2.1.2.4 *MBTD1-PHF1*

Han et al. (2020) reported a case of LG-ESS harboring *MBTD1-PHF1* fusion comprising *MBTD1* exon 16 and 47 bp insertion to *PHF1* exon 2, which is predicted to encode a chimeric protein containing all functional domains of MBTD1 and PHF1 (Table 1).

The MBTD1 protein is a histone H4 lysine 20 methylation (H4K20me) reader (Jacquet et al., 2016), which contains four MBT repeats and a Phe-Cys-Ser (FCS) zinc finger domain (Eryilmaz et al., 2009). Structural analysis showed that MBTD1 engages the NuA4 non-catalytic subunit *EPC1* by the MBT repeats, a site distinct from the H4K20me-binding site. The binding between MBTD1 and *EPC1* facilitates the formation of the intact NuA4 complex and regulates certain gene expression by recruiting the intact NuA4 complex to specific genomic loci (Jacquet et al., 2016; Zhang et al., 2020). However, the chimeric protein MBTD1-PHF1 might directly bridge Piccolo-NuA4

and the PRC2 complex, resulting in diverting the HAT activity of Piccolo-NuA4 to PHF1's normal genomic targets, which is a mechanism similar to that of the EPC1-PHF1. As speculated above, the conformation of MBTD1-PHF1 might disturb the engagement between PHF1 and DNA and impair the HMT activity of PRC2.

2.1.2.5 BRD8-PHF1

The *BRD8-PHF1* fusion gene in LG-ESS forms between exon 16 of *BRD8* from 5q31 and exon 2 of *PHF1* from 6p21 (Table 1). The chimeric transcript retains the entire coding region of *PHF1* but loses the conserved bromodomain sequence from *BRD8* (Micci et al., 2017).

BRD8, a specific accessory subunit of the human NuA4 HAT complex, confers an additional effect to this complex. In addition to linking NuA4 to ligand-dependent transcription regulation by the thyroid hormone receptor (Monden et al., 1997), BRD8 may be implicated in local chromatin retention following the initial recruitment of NuA4 complex (Hassan et al., 2002). The bromodomain of BRD8 is an acetylated lysine-binding domain, whose loss in BRD8-PHF1 could result in the alteration of HAT activity of NuA4 and/or of protein acetylation (Micci et al., 2017). As PHF1 constitutes the 3' end of the BRD8-PHF1 fusion protein, this adds to the likelihood that BRD8-PHF1 shares the same pathogenic mechanism as the other PHF1-related fusion proteins (Table 1).

2.1.3 MBTD1-CXorf67

Dewaele et al. (2014) described the t(X;17)(p11;q21) translocation and *MBTD1-CXorf67* fusion of *MBTD1* exon 16 to exon 1 of chromosome X open reading frame 67 (*CXorf67*, also named *EZHIP* or *CATACOMB*) in LG-ESS (Table 1). The chimeric MBTD1-CXorf67 protein is predicted to contain all functional domains of MBTD1 and the serine-rich region of CXorf67.

The *CXorf67* gene is highly overexpressed in normal oocytes in comparison to its low-level expression in other tissues, including normal endometrium. The *CXorf67* locus exhibits a high degree of DNA methylation, possibly explaining why this gene is not more broadly expressed (Piunti et al., 2019). However, in ESS, the *MBTD1-CXorf67* chromosomal rearrangement results in the ectopic overexpression of the CXorf67 3' portion (Dewaele et al., 2014). One study further established that CXorf67 is a subunit of the PRC2 complex.

Both CXorf67 and the MBTD1-CXorf67 fusion proteins interact with the PRC2 complex and significantly decrease the catalytic products of PRC2, H3K27me2/3 (Piunti et al., 2019). The same study also demonstrated that the high level of CXorf67 protein is the direct cause of PRC2 function inhibition and reduced level of H3K27me2/3 (Piunti et al., 2019). Hübner et al. (2019) demonstrated that the highly conserved peptide sequence located in the C-terminal region of CXorf67 mimics the sequence of K27M-mutated histones and binds to the SET domain of EZH2 in aggressive posterior fossa ependymoma. This interaction blocks EZH2 methyltransferase activity and inhibits PRC2 function, leading to the de-repression of PRC2 target genes.

Piunti et al. (2019) also showed that the chimeric protein MBTD1-CXorf67 interacts not only with the PRC2 subunit EZH2 but also with the NuA4 subunit transformation/transcription domain-associated protein (TRRAP). Thus, similar to MBTD1-PHF1, MBTD1-CXorf67 might divert the nontargeted HAT activity of Piccolo-NuA4 to PRC2's normal genomic targets. Nevertheless, the lack of evidence to date prompts confirmatory research to support this theory.

Overall, all of the above recurrent fusion proteins in LG-ESSs are characterized by the presence of an N-terminal NuA4 component and a C-terminal PRC2 subunit. Most of these fusion proteins retain the majority of the functional domains of partner proteins. It has been demonstrated that certain fusion proteins, such as JAZF1-SUZ12 and MBTD1-CXorf67, preserve the function to bind NuA4 to PRC2. Theoretically, the other fusion proteins might also retain the ability to bind both NuA4 and PRC2. It is now considered that the aberrant fusion proteins drive tumorigenesis in LG-ESSs. While the exact mechanism is unclear, the aberrant acetylation process or methylation process, or both, of specific sites are thought to be the critical events. Results of a meta-analysis of gene expression profiling studies on LG-ESSs confirmed that half of the genes deregulated in LG-ESSs constitute direct targets of SUZ12, and the activation of multiple genes is implicated in Wnt signaling, particularly β -catenin expression in 50%–60% of LG-ESSs. These results suggested shared pathogenetic mechanisms among different rearrangements in LG-ESSs (Przybyl et al., 2018).

2.2 Recurrent gene alterations in HG-ESSs

2.2.1 *YWHAE-NUTM2*

In the current WHO classification, HG-ESSs are solely represented by those harboring t(10;17)(q22;p13) rearrangement leading to the *YWHAE-NUTM2* fusion protein (Table 1) (Ferreira et al., 2018). Emerging evidence suggests that the *YWHAE* gene and its product play versatile roles in cancer development and progression (Liang et al., 2009; Che et al., 2010; Liu et al., 2013; Leal et al., 2016; Yang et al., 2019; Yao et al., 2019; Xu et al., 2020).

Subcellular localization determines the accessibility to potential interacting proteins and the post-translational modification machinery (Hung and Link, 2011). However, the *YWHAE-NUTM2* fusion protein is reported to reside predominantly in the nucleus in HG-ESS (Lee et al., 2012), whereas the endogenous wild-type 14-3-3 ϵ is cytoplasmic (Brunet et al., 2002). Meanwhile, 14-3-3 ϵ in the *YWHAE-NUTM2* fusion protein retains the amino acids necessary for dimerization and phosphoprotein binding (Lee et al., 2012). Most recently, a study showed that the upregulation of epidermal growth factor receptor (EGFR), insulin-like growth factor 1 receptor (IGF1R), platelet-derived growth factor α (PDGF α), and subsequent downstream signalings within the phosphatidylinositol-3-kinase (PI3K)-serine/threonine kinase (AKT) and mitogen-activated protein kinase (MAPK) pathways is associated with increased migration in clear cell sarcoma of the kidney (CCSK) with recurrent t(10;17)(q22;p13) rearrangement (Table 1). Either anti-EGFR, anti-IGF1R, or anti-PDGF α treatment could markedly reduce cell migration (Kenny et al., 2018). It was also verified that the expression of cyclin D1 encoded by the *CCND1* gene is upregulated, whereas diffuse cyclin D1 nuclear immunostaining was considered as a diagnostic immunomarker for *YWHAE-NUTM2* HG-ESS (Kenny et al., 2018).

2.2.2 *BCOR*-related gene alterations

Recently, a group of ESSs harboring both zinc finger CCCH domain-containing protein 7B (*ZC3H7B*)-*BCOR* fusion and internal tandem duplication (ITD) in the last exon of the B-cell lymphoma 6 (*BCL6*) corepressor (*BCOR*) gene were provisionally classified as HG-ESS with an aggressive clinical course (Table 1) (Ferreira et al., 2018).

The *BCOR* protein is a transcriptional corepressor involved in inducing gene silencing via histone modification by either interacting with *BCL6* through the *BCL6*-binding domain, or binding to polycomb group ring finger 1 (*PCGF1*) protein as part of PRC1.1 through the *PCGF* Ub-like fold discriminator (*PUFD*) domain (Ferreira et al., 2018; Astolfi et al., 2019). Oncogene *BCL6* is involved in tumorigenesis, particularly lymphomagenesis. As a non-canonical PRC1 (ncPRC1), PRC1.1 is formed by either *BCOR* or *BCOR-like 1* (*BCORL1*) associated with the histone demethylase lysine demethylase 2B (*KDM2B*). PRC1.1 has additional H2A ubiquitination activity mediated by the heterodimer between the polycomb group (*PcG*) protein ring finger protein 1 (*RING1*)/ring finger protein 2 (*RNF2*) and *PCGF1* (Kommoss et al., 2020a; Wong et al., 2020).

The *ZC3H7B* (also known as *RoXaN*)-*BCOR* fusion gene is formed by the t(X;22)(p11;q13) translocation (Panagopoulos et al., 2013). However, less is known about *ZC3H7B* gene and its product, which contains several domains involved in protein/protein and nucleic acid/protein interactions (Harb et al., 2008; Astolfi et al., 2019). Panagopoulos et al. (2013) reported that the most important role of the *ZC3H7B-BCOR* fusion protein may be in epigenetic regulation through a putative fusion protein retaining multiple functional domains, although additional experiments are required to determine the oncogenetic mechanisms of *ZC3H7B-BCOR* (Table 1).

The *BCOR* ITD alteration involves exon 15 or exon 16 residing within the *PUFD* domain (Chiang et al., 2017; Mariño-Enriquez et al., 2018; Astolfi et al., 2019). Research has pointed out that canonical PRC1 (cPRC1) is recruited to target sites via the PRC2-dependent H3K27me3 marks to stabilize the compacted chromatin, while the *KDM2B*-mediated recruitment of ncPRC1 drives the ubiquitination of Lys119 in histone H2A (H2AK119) that conversely promotes binding of PRC2, leading to chromatin compaction and gene silencing (Ma et al., 2017; Astolfi et al., 2019; Wong et al., 2020). However, *BCOR* ITD hinders *BCOR* binding to *PCGF1* and consequently disrupts the structure and/or function of PRC1.1 in epigenetic modification (Table 1) (Wong et al., 2020).

Similar to HG-ESS with *YWHAE-NUTM2*, cyclin D1 immunoreactivity is strong and diffuse in *BCOR*-related HG-ESS. Additionally, strong *BCOR* expression

is observed not only in the HG-ESSs with *ZC3H7B-BCOR* and *BCOR* ITD but also in the HG-ESSs with *YWHAE-NUTM2* (Chiang et al., 2017; Lewis et al., 2018; Mariño-Enriquez et al., 2018; Cotzia et al., 2019). As reported recently, most soft tissue undifferentiated round cell sarcomas with *YWHAE*, *BCOR* rearrangements, or *BCOR* ITD show neurotrophic tyrosine receptor kinase 3 (*NTRK3*) mRNA upregulation and cytoplasmic pan-Trk immunoreactivity (Kao et al., 2020). Furthermore, the methylation profile of LG-ESS differs from that of HG-ESS, while HG-ESS with *BCOR* rearrangement and HG-ESS with *YWHAE-NUTM2* gene fusion share similar methylation profiles (Kommoss et al., 2020b). These results suggested that HG-ESSs with different rearrangements share the pathogenic mechanisms.

2.3 Additional fusion genes in ESSs without solid evidence

The *MEAF6-SUZ12* fusion gene with no documented 1;17 rearrangement karyotype was identified in an LG-ESS case (Makise et al., 2019). Dickson et al. (2018) described two ESSs harboring *EPC1-SUZ12* and *EPC1-BCOR* fusion genes, which had an aggressive clinical course and predominantly high-grade morphology. Allen et al. (2017) reported a case initially diagnosed as LG-ESS with *JAZF1-BCORL1* fusion featuring splice-site mutation within neurofibromatosis type 1 (*NFI*) and the homozygous deletion of cyclin-dependent kinase inhibitor 2A/B (*CDKN2A/B*). However, according to the available morphological pictures and the aggressive clinical course showed in the literature, Ferreira et al. (2018) believed that this case might have been HG-ESS. In a retrospective study, multiple previously undiscovered *BCOR*-related rearrangements were identified in ESSs, including *BCOR-L3MBTL* histone methyl-lysine-binding protein 2 (*L3MBTL2*), E1A-binding protein p300 (*EP300*)-*BCOR*, *BCOR-NUT* family member 2G (*NUTM2G*), *BCOR-Ral* GEF with PH domain and SH3-binding motif 1 (*RALGPS1*), *BCOR-MAP7* domain-containing 2 (*MAP7D2*), retrotransposon Gag-like 9 (*RTL9*, also referred to as *RGAG1* in the literature)-*BCOR*, *ING3-BCOR*, *BCOR-nuclear* GTPase, germinal center associated (*NUGGC*), lysine methyltransferase 2D (*KMT2D*)-*BCOR*, cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB)-binding protein (*CREBBP*)-*BCOR*, and *BCOR* internal rearrangement.

The implicit biologic potential associated with these fusions remains to be fully characterized (Lin et al., 2020). Obviously, most of the partners involved in the above fusion genes play a role in epigenetic modification, mainly methylation and acetylation (Qin et al., 2012; Attar and Kurdistani, 2017; Froimchuk et al., 2017).

2.4 Molecular alterations in ESSs beyond the recurrent fusion genes

Although recurrent fusion genes are considered as driver events for ESSs development, copy number alterations (CNAs) and point mutations encompassing driver genes might also contribute to the development of ESSs (Choi et al., 2015).

Patel et al. (2020) reported two ESS cases lacking any known rearrangements but featuring a catenin β 1 (*CTNNB1*)-activating mutation and biallelic *CDKN2A* (encoding p16/INK4a)-inactivating mutations, respectively. Mutations in *CTNNB1* activate Wnt-targeted genes and the expression of one such activated Wnt-targeted gene, *CCND1*, is frequently upregulated in ESSs. The *CCND1* gene encodes cyclin D1, which is an allosteric regulator of cyclin-dependent kinase 4 (CDK4) and is required for cell passing through the G1/S checkpoint. As an inhibitor of cyclin D/CDK4 by TCF/ β -catenin pathway, p16/INK4a may also promote cell cycle dysregulation through loss-of-function mutations in *CDKN2A*. Ultimately, the activation of *CTNNB1* and/or repression of *CDKN2A* result in the release of cyclin D/CDK4 inhibition, subsequent passage through the G1/S checkpoint, and cell proliferation. One further case exhibited *CCND2* gene amplification, which encodes cyclin D2, an additional activator of the CDK4 kinase similar to cyclin D1 (Lin et al., 2020). In a recent study, an HG-ESS mouse model, which is positive for cyclin D1, was established by oncogenic *Hras*^{G12V} expression plus *CDKN2A* knock-down (Brandt et al., 2017).

A number of studies indicated that it is not uncommon for the amplification of mouse double-minute homolog 2 (*MDM2*) and *CDK4* plus *CDKN2A* deletion to occur together in ESSs with *JAZF1* rearrangement or *BCOR*-rearrangement (Schoolmeester et al., 2015; Hoang et al., 2017; Kommoss et al., 2020b; Lin et al., 2020). The amplification of chromosome 12q13–15, at which the *MDM2* and *CDK4* genes are both located, may be a key event in tumorigenesis (Patel et al., 2017). As described above, CDK4 plays a critical role

in the passage through the G1/S checkpoint and subsequent cell proliferation (Patel et al., 2020). MDM2 is an important negative modulator of p53 and retinoblastoma (Rb) proteins (Uchida et al., 2005; Wade et al., 2012). Additionally, MDM2 physically associates with PRC2 and enhances stemness-promoting chromatin modifications that are independent of p53 (Wienken et al., 2016).

3 Potential therapeutic strategies for LG-ESSs and HG-ESSs

3.1 Targeting the Wnt signaling pathway

As discussed previously, Wnt signaling is the most significantly activated pathway in LG-ESSs. The presence of β -catenin is an indication of activated Wnt signaling pathway, and the lymphoid enhancer-binding factor 1 (Lef1) transcription factor is one of the main effectors of this pathway. The nuclear expression of β -catenin and Lef1 proteins is highly correlated with LG-ESSs (Przybyl et al., 2018; Patel et al., 2020). Wnt signaling is also involved in HG-ESSs with *BCOR* ITD, *ZC3H7B-BCOR*, and *YWHAE-NUTM2*. As described above, the common feature of HG-ESSs is the strong expression of cyclin D1, which is encoded by the Wnt-targeted gene *CCND1* (Ferreira et al., 2018). Cyclin D1 is the activator of CDK4 kinase that promotes cells to pass through the G1/S checkpoint. Therefore, all available evidence suggests that targeting the Wnt pathway and the downstream effectors, particularly CDK4 kinase, might be beneficial to patients with HG-ESS or LG-ESS.

In addition, it has been demonstrated that LG-ESS cells characteristically express estrogen receptor (ER), and *BCOR*-related HG-ESS cells variably express ER (Conklin and Longacre, 2014; Ferreira et al., 2018). Some studies have further proved the efficacy of hormone therapy for ER-positive ESSs (Serkes et al., 2018; Deshmukh et al., 2019). The National Comprehensive Cancer Network (NCCN) guideline (Abu-Rustum, 2021) also recommends aromatase inhibitors as preferred therapeutic regimens for LG-ESS.

Given that CDK4/6 inhibitors and aromatase inhibitors are both available, either alone or in combination, particularly a CDK4/6 inhibitor in combination with an aromatase inhibitor, the survival of patients with advanced ER-positive breast cancer can be substantially

improved (Mauri et al., 2006; Spring et al., 2020). Thus, a CDK4/6 inhibitor alone or with an aromatase inhibitor should be considered to treat ER-positive LG-ESS and ER-positive *BCOR*-related HG-ESS patients with distant metastases, particularly those resistant to endocrine therapy alone. For ER-negative *YWHAE-NUTM2* HG-ESS, the efficacy of CDK4/6 inhibitor alone or its combination with other agents should also be further explored. One relevant report showed that co-targeting CDK4/6 and MDM2 is a promising approach to overcome intrinsic resistance to CDK4/6 inhibition due to increased p53 stability and subsequent p21 accumulation induced by the MDM2 antagonist (Vilgelm et al., 2019).

3.2 Targeted protein degradation

Aberrant fusion proteins are drivers of the development of both LG-ESSs and HG-ESSs; therefore, it is no doubt that the degradation and elimination of pathogenic fusion proteins should constitute an effective therapeutic strategy. Targeted protein degradation is such a promising therapeutic modality whereby degradation offers the chance for targeted protein removal and the consequent ablation of all of its associated functions. This strategy is particularly suitable for the “undruggable” proteins.

Proteolysis-targeting chimeras (PROTACs) are bifunctional molecules, each comprising a ligand for the targeted protein that is attached to an E3 ligase ligand. Binding the targeted proteins by PROTACs results in the ubiquitination and subsequent degradation of the targeted proteins (Chamberlain and Hamann, 2019; Conway, 2020). It is perceived that no PROTACs against oncogenic fusion proteins in either LG-ESSs or HG-ESSs have been subject to research. However, it has been demonstrated that PROTACs efficiently degrade fusion proteins, such as breakpoint cluster region-Abelson (BCR-ABL) and anaplastic lymphoma kinase (ALK) fusion proteins, and inhibit the proliferation of cancer cells driven by these fusion proteins (Lai et al., 2016; Zhang et al., 2018). Certain very recent studies indicated that EED-targeted PROTACs could degrade not only EED but also EZH2 and SUZ12, thus inhibiting the proliferation of PRC2-dependent cancer cells (Hsu et al., 2020; Potjewyd et al., 2020). The concurrent degradation of EED, EZH2, and SUZ12 by PROTACs is the result of the intimate association among EZH2, EED, and SUZ12 (Potjewyd et al., 2020). Based on the results

discussed above, it seems feasible to explore the roles of PROTACs for treating ESSs with recurrent gene fusions.

3.3 Tyrosine kinase inhibitors

NTRK fusions promote tumorigenesis through the constitutive activation of downstream cell growth and proliferation pathways (Rubin and Segal, 2003). As reviewed by Khotskaya et al. (2017), *NTRK* copy number variations and gene overexpression may have clinical implications in a variety of malignancies. Most recently, Kao et al. (2020) reported that most soft-tissue undifferentiated round cell sarcomas with *YWHAE*, *BCOR* rearrangements, or *BCOR* ITD show *NTRK3* upregulation by RNA sequencing data analysis, and cytoplasmic pan-Trk immunoreactivity was observed in 100% of *YWHAE* rearrangement and 80% of *BCOR* ITD soft tissues round cell sarcomas. Although the effect of targeted therapy, such as entrectinib and larotrectinib, on tumors with NTRK overexpression but without gene rearrangement has not been definitely established, it may be worth investigating.

As established above, the migration advantage of CCSK cells with *YWHAE-NUTM2* fusion protein is abrogated by the inhibition of dysregulated MAPK and PI3K-AKT signaling pathways (Kenny et al., 2018). Moreover, it has been demonstrated that wild *YHAWE* is involved in the MAPK and PI3K-AKT signaling pathways under different contexts (Kim et al., 2014; Castañeda et al., 2017). Therefore, blocking the activation of MAPK and PI3K-AKT signaling pathways might be appropriate treatment for HG-ESS with *YWHAE-NUTM2*. In one example, a metastatic ESS patient with *YWHAE*-family with sequence similarity 22 (*FAM22*) translocation and highly expressed mast/stem cell growth factor receptor (SCFR, also C-KIT) was treated by pazopanib and showed good partial response (Verschoor et al., 2018). The main activity of pazopanib is against vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and C-KIT. Additionally, two case reports featured that a case of C-KIT-positive high-grade ESS and a case of C-KIT-focally-positive low-grade ESS exhibited objective responses to imatinib mesylate (Salvatierra et al., 2006; Kalender et al., 2009). The main action of imatinib mesylate is against BCR-ABL tyrosine kinase, platelet-derived growth factor (PDGF), stem cell factor (SCF), and C-KIT. The effectiveness of imatinib mesylate and

pazopanib triggered studies exploring the expression of C-KIT and PDGFR in ESSs. It was shown that ESSs harboring the *YWHAE-FAM22* fusion gene frequently overexpress C-KIT (Lee CH et al., 2014). Cossu-Rocca et al. (2012) reported that 68% and 36% of ESSs overexpress PDGFRA and PDGFRB, respectively. It is known that both PDGFR and C-KIT are upstream members of the MAPK and PI3K-AKT signaling pathways. Consequently, the effect of tyrosine kinase inhibitors targeting C-KIT, PDGFR, and downstream MAPK and PI3K-AKT signaling pathways in ESSs should be further explored, since the mentioned evidence is from a few small case series due to the rarity of this disease.

3.4 Targeting epigenetic modification

Although tumorigenesis in LG-ESS and HG-ESS is closely associated with recurrent gene alterations, the exact mechanism remains unclear. As mentioned above, the most common speculation is that the tumorigenesis of LG-ESS is attributed to the insufficient HMT activity of PRC2 complex and/or nontargeted HAT activity to PRC2's normal genomic targets, resulting in imbalance between histone methylation and acetylation, and subsequent signaling pathway disturbance. However, to the best of our knowledge, no direct evidence of epigenetic modification for ESSs has supported the above speculation. With regards to HG-ESSs, little is known about the roles of *YWHAE-NUTM2*, *ZC3H7B-BCOR*, or *BCOR* ITD in epigenetic modification and tumorigenesis in HG-ESSs.

In fact, some clinical studies have explored the relationship between the level of HDAC expression and the survival of patients with ESS (Hrzenjak et al., 2006; Baek et al., 2016), and certain in vitro studies have investigated the effect of HDAC inhibitor alone, or combined with other agents, on ESS cells (Hrzenjak et al., 2006; Fröhlich et al., 2014; Quan et al., 2014). These results suggested that inappropriate acetylation is indeed involved in the genesis and development of ESSs, and that targeting the status of histone acetylation might be beneficial. Nonetheless, these results are not closely associated with the mechanism of genesis or development of ESSs as speculated above.

Concerning the modification of histone methylation status in ESSs, Hashizume et al. (2014) indicated that the pharmacologic inhibition of K27 demethylase Jumonji domain-containing protein 3 (JMJD3) increases

cellular H3K27 methylation in K27M tumor cells. As previously discussed, MBTD1-CXorf67 fusion protein only mimics the role of sequence of K27M mutated histones, while, regrettably, no further solid evidence is available on this subject.

Based on the above considerations, it is difficult to get a definite answer to whether targeting epigenetic modification could cure or improve the outcomes of ESSs with recurrent gene alterations. Much more research is therefore needed to explore the relationships among fusion proteins, epigenetic alterations, and ESSs. The approach of ESS treatment via modifying the status of histone methylation and/or histone acetylation by epigenetic agents alone or combined with other agents, however, still constitutes an essential and valid research direction.

4 Conclusions

As advanced LG-ESS and HG-ESS are rare types of tumors, there is an unmet clinical need for systematic therapy for these conditions. This review summarizes the structural and molecular characteristics of these recurrent aberrant proteins in LG-ESSs and HG-ESSs, and concludes their shared pathogenic signaling pathways, as well as potentially actionable targets for LG-ESSs and HG-ESSs. A few therapeutic strategies are proposed based on the above information, although considerably more research is required to identify the feasibility of such strategies. Meanwhile, additional fundamental research to further identify the roles of these recurrent aberrant proteins in the molecular pathophysiology of LG-ESSs and HG-ESSs would benefit the improved classification of ESSs and the development of new therapeutic strategies for these tumor types.

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Author contributions

Chunhong WANG conducted this review. Chunhong WANG and Chunhui LI contributed to the writing and editing of the manuscript. Both authors have read and approved the final manuscript and, therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Chunhui LI and Chunhong WANG declare that they have no conflict of interest.

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