Acta Pharmaceutica Sinica B 2024;14(4):1494−1507

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com

REVIEW

Strategies that regulate LSD1 for novel therapeutics

Meng Li[a,†], Mengge Dai[a,†], Bing Cheng[a], Shaotong Li[a], Enhui Guo[a], Junwei Fu[a], Ting Ma[a,d,*], Bin Yu[a,b,c,d,e,*]

[a]*School of Pharmaceutical Sciences & Key Laboratory of Advanced Drug Preparation Technologies, Ministry of Education, Zhengzhou University, Zhengzhou 450001, China*
[b]*College of Chemistry, Zhengzhou University, Zhengzhou 450001, China*
[c]*Tianjian Laboratory of Advanced Biomedical Sciences, Institute of Advanced Biomedical Sciences, Zhengzhou University, Zhengzhou 450000, China*
[d]*Pingyuan Laboratory, State Key Laboratory of Antiviral Drugs, Henan Normal University, Xinxiang 453007, China*
[e]*State Key Laboratory of Pharmaceutical Biotechnology, Nanjing University, Nanjing 210023, China*

Received 19 August 2023; received in revised form 5 December 2023; accepted 6 December 2023

KEY WORDS

LSD1 regulation;
Transcription repression;
Transcription activation;
the Corepressor complex;
Post-transcriptional modifications;
Metabolites

Abstract Histone methylation plays crucial roles in regulating chromatin structure and gene transcription in epigenetic modifications. Lysine-specific demethylase 1 (LSD1), the first identified histone demethylase, is universally overexpressed in various diseases. LSD1 dysregulation is closely associated with cancer, viral infections, and neurodegenerative diseases, etc., making it a promising therapeutic target. Several LSD1 inhibitors and two small-molecule degraders (UM171 and BEA-17) have entered the clinical stage. LSD1 can remove methyl groups from histone 3 at lysine 4 or lysine 9 (H3K4 or H3K9), resulting in either transcription repression or activation. While the roles of LSD1 in transcriptional regulation are well-established, studies have revealed that LSD1 can also be dynamically regulated by other factors. For example, the expression or activity of LSD1 can be regulated by many proteins that form transcriptional corepressor complexes with LSD1. Moreover, some post-transcriptional modifications and cellular metabolites can also regulate LSD1 expression or its demethylase activity. Therefore, in this review, we will systematically summarize how proteins involved in the transcriptional corepressor complex, various post-translational modifications, and metabolites act as regulatory factors for LSD1 activity.

*Corresponding authors.
E-mail addresses: mating@zzu.edu.cn (Ting Ma), zzuyubin@hotmail.com (Bin Yu).
[†]These authors made equal contributions to this work.
Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2024.01.005

1. Introduction

The alteration of hereditary substance DNA significantly affects tumorigenesis[1]. If the gene expression changes but is not involved in DNA sequences, this regulation manner is referred to as epigenetic modification[2]. Epigenetic regulation has three categories: DNA methylation, non-coding RNAs, and histone post-transcriptional modification. Among them, histone post-transcriptional modification is a vital regulation mechanism[2,3]. There are many kinds of histone modifications, such as methylation, phosphorylation, acetylation, and ubiquitination. As the first histone demethylase, LSD1 displays a dominant role in many physiological processes.

1.1. The structure of LSD1

In terms of structure, LSD1 protein consists of three domains: a SWIRM domain located at the amino terminus, an AOL domain containing flavin adenine dinucleotide, and another coiled-coil TOWER domain[4−6]. Usually, LSD1 regulates gene expression mainly through three pathways: (1) binding to target genes through the transporter-SNAT2 domain of REST corepressor 1 (RCOR1/CoREST), causing demethylation of H3K4 and ultimately leading to transcriptional repression; (2) binding to androgen receptor[7,8] or estrogen receptor[9] and demethylating H3K9, resulting in hormone receptor-dependent gene transcription activation; (3) demethylating H3K4, LSD1 enables DNA methyltransferases 3 like protein, a positive regulator of DNA methyltransferases, to bind to the unmethylated K4 site, and thus promoting the expression of DNA methyltransferases and indirectly causing DNA re-methylation, finally leading to gene transcriptional repression. In most situations, LSD1 demethylates the monomethyl (me1) or dimethyl (me2) of H3K4 or H3K9, depending on its interacting partners[10−15].

Although LSD1 was initially identified as a demethylase, studies have highlighted the roles of LSD1 in regulating non-histone activity through LSD1-dependent demethylation[16−18]. The demethylase activity of LSD1 can change the function and stability of some non-histone proteins, such as forkhead box A1[19], DNA methyltransferase 1[20], signal transducer and activator of transcription 3[21], p53[22,23], E2F transcription factor 1[24], argonaut 2[25], recombinant retinoblastoma 1[26], metastasis-associated gene 1[27], hypoxia-inducible factor-1α (HIF-1α)[28−30], etc. There is no sequence similarity between these non-histone and histone substrates, which suggests that the interacted partners are crucial in the demethylation process[10].

1.2. The function of LSD1

LSD1 plays a fundamental and diverse role in immune regulations and pathological processes such as cancers and infections[25,31−38]. LSD1 dysregulation is tightly related to vicious transformation, epithelial-mesenchymal transition (EMT), cell multiplication, and differentiation[39]. Moreover, LSD1 overexpression is associated with poor prognosis for cancer patients. Analysis of various tumor tissue gene expressions from the UCSC Xena (https://xena.ucsc.edu) revealed that the expression of the *LSD1* gene in most tumor tissues is higher than that in adjacent normal tissues. In addition, among of the many different kinds of tumors, bone cancers, cervical cancer, leukemia and neuroblastoma have a relatively higher expression than other cancers (Fig. 1). As reported, LSD1 is overexpressed in cervical cancer and leukemia, and LSD1 silencing enhances immunotherapy by decreasing the expression of CD47 and programmed cell death 1 ligand 1 in cervical cancer[40]. Moreover, targeting LSD1 can induce acute myeloid leukemia (AML) cell differentiation by down-regulating the chromatin protein gse1 coiled-coil protein[41,42]; but phosphorylation of LSD1 at the serine 112 site induces EMT and metastasis in breast cancer[43]. Of note, many developed LSD1 inhibitors are currently used in those LSD1 highly expressed cancers such as AML[44]. Taken together, it is believed that LSD1 acts as a promising therapeutic target for treating cancers.

2. Various manners that regulate LSD1

As described above, LSD1 takes part in the progression of many diseases, and targeting LSD1 can achieve excellent results. Therefore, numerous inhibitors have been developed to inhibit its expression or activity by targeting LSD1 directly. Given that many LSD1 inhibitors have been reported, herein we mainly summarize LSD1 inhibitors that are currently being investigated in clinical trials[31,45−51]. To date, irreversible inhibitors such as tranylcypromine, IMG-7289, INCB059872, GSK-2879552, ORY-1001, ORY-2001, TAK-418, LH-1802 and reversible inhibitors SP-2577 and CC-9001 have entered clinical trials (Fig. 2). Tranylcypromine is an LSD1 inhibitor and is currently being evaluated for its effect alone or in combination with other drugs on myelodysplastic syndrome (MDS) or AML patients[51,52]. Similarly, ORY-1001 is a highly potent and selective covalent LSD1 inhibitor in phase I/II clinical trials and tested for its safety, pharmacodynamics, and maximum tolerated dose in relapsed or refractory small cell lung carcinoma (SCLC) and AML patients[51,53,54]. ORY-2001 is the only LSD1 and MAO-B dual-targeting inhibitor that is evaluated for its tolerability and efficacy in individuals with borderline personality disorder and Alzheimer's disease[51,55]. Unfortunately, GSK2879552 has been discontinued clinical trials due to its poor disease control and high incidence of adverse effects[51,56]. INCB059872 is designed to test its safety, tolerability, and efficacy in patients with advanced malignancies, sickle cell disease, solid tumors, and relapsed or refractory Ewing sarcoma[51]. Since 2018, IMG-7289 has been investigated in several clinical studies for treating myelofibrosis, myeloid malignancies, SCLC and so on[42,51]. In particular, as a small molecule LSD1 inhibitor, TAK-418 (Takeda, Japan) is evaluated for safety, tolerability, and pharmacokinetics primarily in healthy subjects but terminated finally[51]. Moreover, LH-1802, developed by Professor Liu and collogues, and its proposed indications are hematological or solid tumors. Currently, it has entered clinical phase I studies for the treatment of relapsed or refractory AML and MDS[57]. In addition to irreversible LSD1 inhibitors, CC-90011 is the first reversible LSD1 inhibitor that is currently undergoing clinical evaluation in SCLC, relapsed or

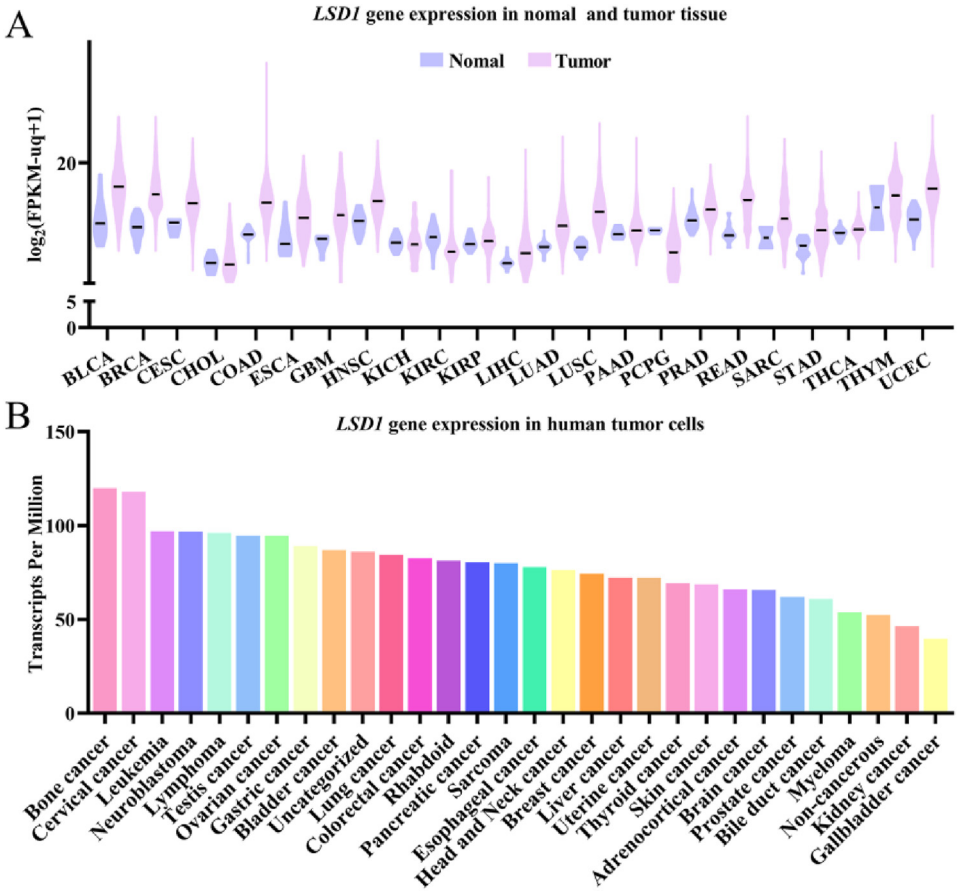

Figure 1 *LSD1* gene expression in different cancers. (A) The *LSD1* gene expression in diverse tumor tissues and adjacent normal tissues. (B) *LSD1* mRNA expression in various human tumor cells measured by transcripts per million. BLCA: bladder urothelial carcinoma; BRCA: breast invasive carcinoma; CESC: cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL: cholangio carcinoma; COAD: colon adenocarcinoma; ESCA: esophageal carcinoma; GBM: glioblastoma multiforme; HNSC: head and neck squamous cell carcinoma; KICH: kidney chromophobe; KIRC: kidney renal clear cell carcinoma; KIRP: kidney renal papillary cell carcinoma; LIHC: liver hepatocellular carcinoma; LUAD: lung adenocarcinoma; LUSC: lung squamous cell carcinoma; PAAD: pancreatic adenocarcinoma; PCPG: pheochromocytoma and paraganglioma; PRAD: prostate adenocarcinoma; READ: rectum adenocarcinoma; SARC: sarcoma; STAD: stomach adenocarcinoma; THCA: thyroid carcinoma; THYM: thymoma; UCEC: uterine corpus endometrial carcinoma.

refractory solid tumors, and non-Hodgkin's lymphoma patients[58]. Another reversible LSD1 inhibitor SP-2577 is evaluated for its safety and tolerability in patients with advanced solid tumors, small cell ovarian cancer, relapsed or refractory Ewing sarcomas, etc.[59]. Encouraged by these LSD1 inhibitors in the clinical stage, more effective and less toxic inhibitors are still needed to develop to conquer human diseases where LSD1 is dysregulated.

However, LSD1 can form kinds of corepressor complexes with some proteins, and changing the stability of corepressor complex elements also affects the expression of LSD1. In addition, there are many reports that LSD1 expression could also be influenced by post-transcriptional modifications. And some other metabolites can also regulate LSD1 expression (Fig. 3). Therefore, in the following section, we will summarize the proteins and other factors that can affect LSD1 and provide perspectives for developing novel lead compounds to restrain its expression.

2.1. Regulation of LSD1 expression or activity by modulating corepressor complex components

LSD1 can form different corepressor complexes with many proteins such as histone deacetylases (HDACs), RCOR1, BRAF35–HDAC complex protein (BHC80, also known as Ph.D. finger protein 21A, an abbreviation for PHF21A), HMG box-containing protein 20B, and the Krüppel-like zinc finger protein 217 (ZNF217) and so on[60]. HDACs are proteases that play a crucial role in modifying chromosome structure and regulating gene expression. Specifically, HDAC1 and HDAC2 are found in multiprotein corepressor complexes like the Sin3 complex and NuRD complex. Additionally, they can be recruited to chromatin regulatory regions by certain transcription factors such as specificity protein 1 (Sp1), specificity protein 3 (Sp3), nuclear factor kappa-B (NF-κB), and yin-yang-1 (YY1), thus exhibiting various functions[61]. For RCOR1/CoREST, it is a component of the multiunit LSD1 complex, which modifies nucleosomes by deacetylation and demethylation to suppress gene transcription. Moreover, LSD1 and RCOR1 can bind to each other directly[62]. Expressed in nerve and non-nerve cells, BHC80 is a skeleton protein of the BRAF-histone deacetylase (BHC) complex. In non-nerve cells, BHC80 can participate in the transcriptional repression of nerve-specific genes and change the transcriptional state of the target genes promoter from activation to repression[63]. HMG box-containing protein 20B is a member of the high-mobility group which is associated with chromatin. It is found in the nucleus of eukaryotes

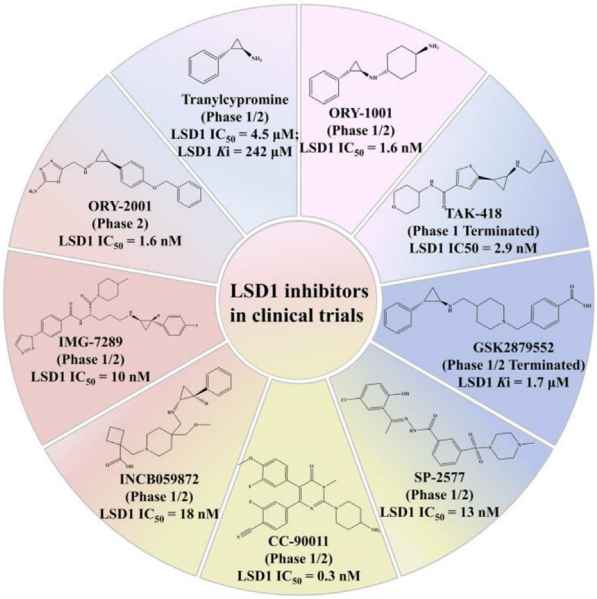

Figure 2 LSD1 inhibitors in clinical trials. M, mol/L.

and plays a role in regulating gene transcription. This regulation occurs through modifying, bending, or altering the structure of chromatin/DNA to facilitate the formation of macromolecular complexes containing various protein factors[64]. Moreover, ZNF217 is an oncogene located at chromosome 20q13.2[65,66]. Overexpressed ZNF217 can recruit LSD1 to affect the epigenetic regulation of CDH1 at the transcriptional level, leading to the promotion of EMT and subsequent stimulation of hepatocellular carcinoma metastasis[67]. Therefore, the activity of LSD1 could be modulated by affecting the interacted proteins with LSD1[15,63]. So, we described the mechanisms of how these core component proteins could regulate LSD1.

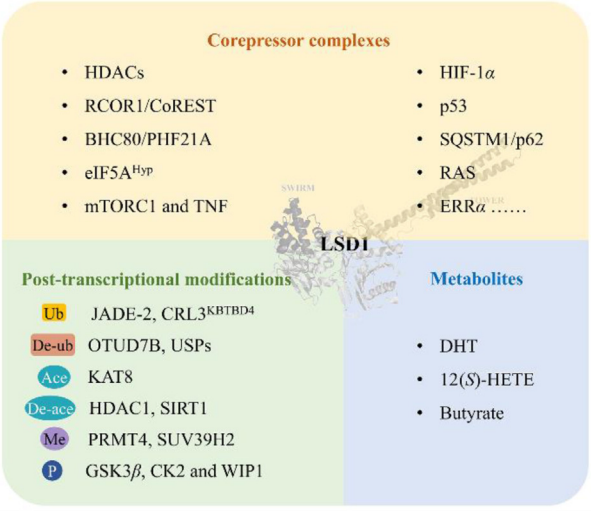

Figure 3 The structure and different regulatory factors of LSD1. LSD1 expression or activity can be regulated by changing the expressions of corepressor complexes proteins, such as HDACs, RCOR1/CoREST, BHC80/PHF21A, eIF5A^{Hyp}, HIF-1α, p53, SQSTM1/p62, RAS and so on. And LSD1 stability is also regulated by enzymes related to post-transcriptional modifications, such as ubiquitination enzymes JADE-2 and CRL3^{KBTBD4}, de-ubiquitination enzymes OTUD7B and USP7/17/22/28/38, KAT8, deacetylases HDAC1 and SIRT1, methyltransferases PRMT4 and SUV39H. In addition, some metabolites can also affect LSD1 expression, such as DHT, 12(*S*)-HETE and butyrate.

2.1.1. *eIF5A^{Hyp}*

Eukaryotic translation initiation factor 5A (eIF5A) is the only protein that contains hypusine in eukaryotic cells, and the hypusination of eIF5A (eIF5A^{Hyp}) is an essential post-translational modification for its activity, which is catalyzed continuously by deoxyhypusine synthase enzyme and deoxyhypusine hydroxylase enzyme[68–70]. Li et al.[71] revealed that Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) could directly activate ornithine decarboxylase 1 (ODC1) in the polyamine biosynthesis pathway and promote the secretion of polyamine. Then elevated polyamine levels catalyzed the generation of eIF5A^{Hyp}, which was required to translate LSD1 efficiently. The increased LSD1 protein reduced the methylation level of H3K4me1/2, thus inhibiting the expression of downstream antioncogenes, such as growth arrest specific 1, programmed cell death 4, and forkhead box A2, and promoting cell proliferation and tumor growth (Fig. 4).

2.1.2. *BHC80*

BHC80, a plant homeodomain (PHD) finger-like protein, directly interacts with LSD1 and affects its activity[72]. While LSD1 actively demethylates H3K4 on free histones *in vitro*, adding BHC80 will significantly inhibit its activity. BHC80 also shows the same inhibitory activity on the nucleosome substrate against LSD1[63]. Collectively, the BHC80 protein can bind to LSD1 to form a complex and inhibit the demethylase activity of LSD1 (Fig. 4).

2.1.3. *RCOR1*

RCOR1 is a protein that acts as a corepressor of the RE1 silencing transcription factor[73]. Some researchers have reported that LSD1 can form a stable complex with RCOR1 protein, and the two proteins combine directly with each other[74,75]. This complex exhibits potent H3K4 demethylase activity, and RCOR1 is required for LSD1 to mediate the demethylation modification of nucleosome substrates[74,75]. In addition, it has also been reported that depletion of RCOR1 promotes the degradation of LSD1, leading to a decreased expression level of LSD1 in HeLa cells[63]. Moreover, some previous studies have also demonstrated the tight and specific interaction between 286 and 482 fragments of RCOR1 (RCOR1$^{286-482}$) and LSD1[76–78]. RCOR1 grants LSD1 the ability to demethylate nucleosome substrates *in vitro* and protects LSD1 from proteasomal degradation *in vivo*[63]. Given the importance of RCOR1 in guiding the demethylation of specific nucleosome substrates and the compact interaction between RCOR1 and LSD1[79], LSD1 activity could be inhibited by regulating RCOR1. However, the mechanisms by which RCOR1 affects LSD1 activity need to be further explored (Fig. 4).

2.1.4. *p62*

As a multifunctional ubiquitin-binding protein, p62 can interact with various proteins to regulate many signaling and cellular activities[80]. It has been reported that p62 preferentially recognizes the lysine 63 (K63)-linked poly-Ub chains and shuttles substrates for proteasomal degradation[81]. LSD1 ubiquitination has become an essential regulatory way for its turnover[82], and it is mainly

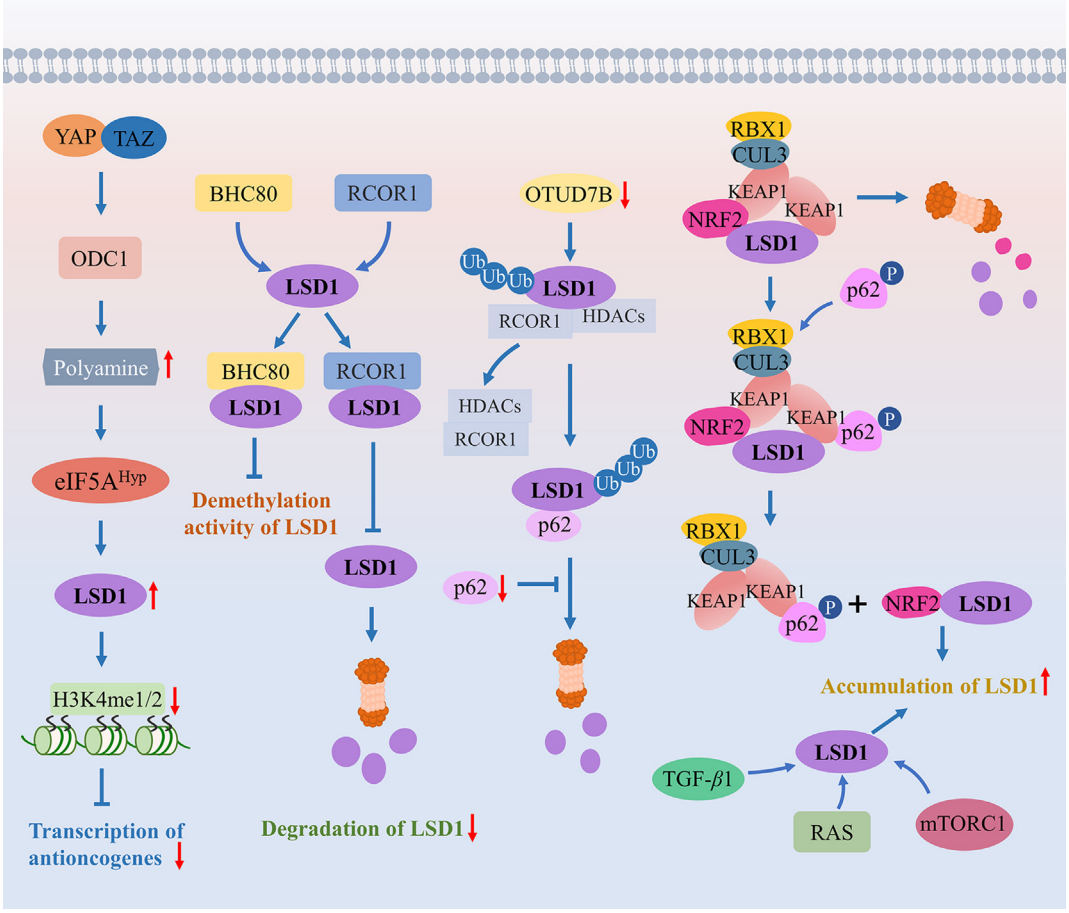

Figure 4 The mechanisms of how eIF5A^{Hyp}, BHC80, RCOR1, mTOC1, RAS, and TGF-β1 regulate LSD1 expression. (1) Polyamine controls LSD1 protein level by mediating eIF5A^{Hyp} modification. After YAP combines with TAZ, ODC1 is activated to promote the secretion of polyamine, and eIF5A^{Hyp} production is catalyzed by deoxyhypusine synthase and deoxyhypusine hydroxylase, which promotes LSD1 protein translation, inhibiting downstream target genes. (2) BHC80 and RCOR1 respectively form complexes with LSD1 to inhibit the activity or degradation of LSD1. (3) Under normal conditions, p62 directly interacts with ubiquitinated LSD1 to cause its degradation; but under the oxidative stress condition, the p-p62 is triggered, and LSD1 protein is subsequently released from the p-p62−KEAP1−CUL3−E3 complex to facilitate its accumulation. (4) TGF-β1, RAS and mTORC1 also induce LSD1 expression accumulation.

biased towards K63-linked poly-Ub chains at lysine 226/277 residues. However, K63-linked Ub chains usually do not have proteolytic functions[83]. Increasing evidence has shown that the function of LSD1 relies on its connection to diverse elements, including RCOR1 and HDACs[76]. The OTU domain containing 7B (OTUD7B) deficiency increased the K63-linked ubiquitination degradation of LSD1, which disrupted the integrity of the LSD1/RCOR1/HDACs complex. Strikingly, the OTUD7B defect promoted the association of LSD1 with p62 and targeted LSD1 for p62-mediated proteasomal degradation, thereby eliminating breast cancer metastasis. By contrast, the knockdown of p62 completely blunted the degradation of LSD1 aroused by OTUD7B loss[84] (Fig. 4). p62 displays a critical effect on the proteasomal degradation of LSD1, which affects the homeostatic and biological function of LSD1.

Moreover, it is widely known that p62 is involved in the nuclear factor erythroid 2-related factor 2−kelch-like ECH-associated protein-1 (NRF2−KEAP1) pathway[85]. NRF2 is a transcription factor consisting of seven Neh domains and each has its specific function. For example, the Neh2 domain mediates the interaction with KEAP1[86]. KEAP1 is a substrate adaptor protein of cullin3 (CUL3)-dependent E3 ligase complex, which can be assembled with CUL3 and RBX1 into a functional KEAP1−CUL3−E3 complex to regulate NRF2[87]. NRF2−KEAP1−CUL3−E3 could form a complex with LSD1 and p62. Exposure to oxidative stress, such as high glucose concentrations, can trigger the phosphorylation of p62 (p-p62) at S349. Then it is more advantageous for p62 to interact with KEAP1−CUL3−E3, thus facilitating the NRF2−LSD1 complex to be released from the KEAP1 proteasome complex[85] (Fig. 4). Through this manner, p-p62 can lead to the development of endometrial cancer through repressing LSD1 ubiquitination.

2.1.5. *p53*

p53 interacts directly with LSD1 *in vivo* and *in vitro*, resulting in reciprocal functional modifications[88]. LSD1 can specifically demethylate the di-methylation of p53 at the lysine 370 site, making p53 a mono-methylation state[22]. In addition, it has also been revealed that the expression of LSD1, which bound the chromatin at specific sites, was reduced in p53-null cells, thus decreasing the demethylation level of H3K4me2 and leading to *p21* and alpha-fetoprotein gene activation[88,89]. Collectively, the mutual binding

of LSD1 and p53 leads to the conversion from di-methylation to mono-methylation at the lysine 370 site of p53, which in turn enhances the enzymatic activity of LSD1.

2.1.6. *mTORC1 and TNF*

The mammalian target of rapamycin (mTOR) is a significant target for tumor therapy, and mTORC1 is one of the most studied proteins[90]. Unlike mTORC1, tumor necrosis factor (TNF) is the proinflammatory cytokine, and receptor activator of nuclear factor (NF)-κB-ligand (RANKL) is a critical cytokine in the process of osteoclast differentiation and survival[91]. Human osteoclast precursor cells were stimulated by soluble RANKL and TNF, respectively. It was found that RANKL induced significant expression of LSD1 through the mTORC1-dependent activity, and LSD1 expression was also significantly up-regulated after TNF stimulation. Therefore, the expression of LSD1 is induced in the presence of mTORC1 and TNF in human osteoclast precursor cells (Fig. 4).

2.1.7. *HIF-1α*

HIF-1α plays a key role in cell adaptation to changes in oxygen levels. It is continuously synthesized but quickly degraded through acetylation under normal oxygen conditions[92]. HDAC2 plays a key role in regulating HIF-1α stability[93]. Qin and colleagues[94] reported that LSD1 controlled the stability of HIF-1α in an acetylation-dependent way by interacting with HDAC2, and the stability of HIF-1α conversely led to the upward adjustment of LSD1 in the transcription level and the protein level, therefore sustaining an uncontrolled proliferation of pancreatic cancer cells. Moreover, LSD1 regulated osteoclast differentiation *via* stabilizing HIF-1α in normal oxygen conditions through E2F transcription factor 1 activity[91]. In conclusion, LSD1 and HIF-1α can form a positive feedback loop during the maintenance of the hypoxia microenvironment and glucose metabolism conversion.

2.1.8. *RAS*

The oncogenic factor rat sarcoma (RAS) is a pivotal regulator in signaling pathways that control normal cell growth and malignant transformation. Upon conditional activation of RAS, LSD1 overexpression would be induced. Thereby, the accumulation of LSD1 at the promoter and enhancer domains of PI3K interacting protein 1 was increased, suppressing PI3K Interacting Protein 1 transcription and reactivating the PI3K pathway in cancer cells[95] (Fig. 4).

2.1.9. *NRF2*

As described above, NRF2−LSD1−KEAP1−CUL3−E3 could form a complex under normal conditions. Moreover, NRF2 would enhance the interaction of LSD1 and the KEAP1−CUL3−E3 complex. Altogether, LSD1 is degraded through the KEAP1−CUL3−E3 complex to keep it at a relatively low level[85].

2.1.10. *ERRα*

Estrogen-related receptor α (ERRα) and LSD1 interact with each other at the transcriptional start site. In particular, nuclear respiratory factor 1 (NRF1) is an LSD1-tethering factor, and NRF1 was the only factor responsible for recruiting LSD1 to the transcriptional start site in the nucleus[96]. Moreover, ERRα induced LSD1 to specifically demethylate H3K9me2 through demethylation in a dose-dependent manner[97]. ERRα, rather than NRF1, positively modulates the demethylase activity of LSD1, and ERRα−LSD1 promotes cell invasion in a matrix metalloprotease 1-dependent manner.

2.1.11. *TGF-β1*

In addition to ERRα, LSD1 can be regulated by transforming growth factor-β1 (TGF-β1)[98], which plays various cytological roles, including the regulation of cell growth, differentiation, and apoptosis. The specific mechanism was that TGF-β1 up-regulated LSD1 expression to activate the downstream ERK/p65 signaling pathway and promoted the nuclear transfer of p65, increasing the proliferation of gastric cancer cells (Fig. 4).

2.2. *Regulation of LSD1 stability by various post-transcriptional modifications*

The ubiquitin−proteasome pathway is the most common way for protein degradation[99]. Ubiquitin (Ub) molecule is a small protein responsible for labeling specific proteins to be degraded[100]. In the first step, ubiquitin-activating enzyme (also known as E1 enzyme) hydrolyzes ATP to lead to the adenylation of one Ub molecule[101], followed by transferring the adenylated Ub successfully to a cysteine residue in the active center of the E1 enzyme. In the second step, the activated Ub molecule is transferred to a cysteine residue of ubiquitin-conjugating enzyme (also known as E2 enzyme). In the third step, the highly conserved ubiquitin ligase (E3 enzyme) recognizes the specific target protein. It catalyzes the transfer of multiple Ub molecules to the target protein to promote ubiquitination degradation. The target protein is generally covalently linked to the polyubiquitin chain under the sequential action of E1, E2, and E3 enzymes. Finally, it is purposefully identified by the 26S proteasome and degraded into small peptides[102,103]. It has been reported that the ubiquitylation process can be reversed by some proteases called deubiquitylation enzymes (DUBs)[104]. DUBs are proteins that deter ubiquitination by shearing polyubiquitin or monoubiquitin, thereby enhancing the stability of its particular target protein[105]. As reported, LSD1 can be degraded through some E3 ubiquitin ligases, such as JADE Family PHD Finger 2 (JADE-2/PHF16) and Cullin3−E3 ubiquitin ligase Kelch repeat and BTB domain-containing protein 4 ($CRL3^{KBTBD4}$)[106,107]. However, the ubiquitination and degradation process of LSD1 can be reversed by deubiquitylation enzymes such as OTUD7B, ubiquitin-specific protease 7 (USP7), ubiquitin-specific protease 17 (USP17), ubiquitin-specific protease 22 (USP22), ubiquitin-specific protease 28 (USP28) and ubiquitin-specific protease 38 (USP38)[108−111], leading to improved stability and increased expression. Therefore, the LSD1 activity is balanced under the cooperative regulation of ubiquitination and de-ubiquitination enzymes.

Acetylation of lysine in histone tails is highly dynamic and essential for the regulation of chromatin structure, transcription, and DNA repair[112]. Two competing enzyme families, histone lysine acetyltransferases (HATs) and HDACs, regulate histone acetylation[113]. Three prominent HATs have been well studied in humans: glycine-*N*-acyltransferase (HAT1, GCN5, KAT2B), MYST (TIP60, males-absent on the first protein, KAT6A, KAT7), and p300/CBP. There are four categories of HDACs in mammals: Class I (HDAC 1, 2, 3, 8) is widely expressed in human cell lines and nuclear tissues; Class II (HDAC 4, 5, 6, 7, 9 and 10) exhibits tissue-specific expression and can shuttle between the nucleus and cytoplasm; Class III or sirtuins (SIRT1−7), dependent on NAD^+, has a unique catalytic mechanism for deacetylation compared to other HDACs; Class IV has only one confirmed member, HDAC11. HDAC11 can deacetylate different histone sites, resulting in low substrate specificity and, in some cases, functional redundancy[114]. Like HATs, HDACs have several non-histone substrates, such as p53, HSP90, TCF, and β-catenin, to

regulate protein stability, DNA binding, enzyme activity, or protein localization.

Many studies have revealed that histone ubiquitination, methylation, acetylation, and phosphorylation are dynamically regulated processes. Moreover, some of these modifications can inhibit LSD1 expression and its enzyme activity. Therefore, in the next section, we summarized the enzymes that can ubiquitinate/deubiquitinate, acetylate/deacetylate, methylate, and phosphorylate LSD1.

2.2.1. *JADE-2-mediated ubiquitination*

It has been reported that JADE-2 is a typical E3 ubiquitin ligase and could promote LSD1 degradation[115]. This finding was further confirmed in a study that used affinity purification and mass spectrometry to identify the interaction between JADE-2 and LSD1 protein *in vivo*. Moreover, *in vivo,* ubiquitination assays in embryonic stem cells showed that depletion of JADE-2 resulted in a dramatic downregulation in LSD1 polyubiquitination. JADE-2-mediated LSD1 elimination increased the levels of H3K4me1/2, thereby regulating several LSD1 target genes associated with neurogenesis, including pair box 3, zic family member 4, neurogenin 1, and tropomyosin 1, leading to enhanced expression of neural progenitor markers nestin, sox1, and mature neuron markers βIII-tubulin, growth associated protein-43, microtubule associated protein 2 in nervous system development and neuroblastoma differentiation. JADE-2-mediated LSD1 polyubiquitination promoted the differentiation of embryonic stem cells toward neural progenitor cells (Fig. 5)[106]. Therefore, JADE-2 reduces the protein level of LSD1 through post-transcriptional regulation, which may serve as a potential target for the therapeutic intervention of neuroblastoma.

2.2.2. *$CRL3^{KBTBD4}$-mediated ubiquitination*

Sauvageau et al.[116] found that the small-molecule degrader UM171 enhanced the activity of the CRL3 complex, whose target was determined explicitly by KBTBD4. UM171 induced the activation of $CRL3^{KBTBD4}$, which could target the LSD1−RCOR1 corepressor complex and degrade LSD1 by 26S proteasome, which then enhanced the expansion of hematopoietic stem cells and maintained the self-renewal ability of human hematopoietic stem cells *in vitro*[107,117]. This suggests that LSD1 is a natural substrate of the $CRL3^{KBTBD4}$ E3 ligase complex (Fig. 5).

2.2.3. *OTUD7B-mediated de-ubiquitination*

Considering that the ubiquitination process is reversible, some DUBs are found to reverse the ubiquitination degradation of the LSD1 protein. Among the DUBs, OTUD7B is a deubiquitinating enzyme that belongs to the DUBs OTU family, and the increased level of OTUD7B mRNA is frequently found in human cancers[118]. As described earlier, LSD1 protein could be connected with K63-linked poly-Ub chains and is known to perform epigenetic regulation by constituting a corepressor complex with RCOR1/HDACs. The de-ubiquitination assay *in vitro* verified that the recombinant OTUD7B could reduce the level of K63-linked poly-Ub chains ofLSD1 through interacting directly with LSD1, thus increasing the association between LSD1 and RCOR1/HDACs. Thereby dynamically maintaining LSD1/RCOR1/HDACs complex integrity can enhance the demethylation of H3K4me1/2 and H3K9me1/2 and induce the metastasis of breast cancer[84] (Fig. 5). OTUD7B is a bona fide LSD1 de-ubiquitinase that controls its turnover.

2.2.4. *Ubiquitin-specific protease-mediated de-ubiquitination*

Like OTUD7B, USP7[119], USP22[120], USP17, USP28[121], and USP38[108] can also remove polyubiquitin chains on LSD1 and stabilize its intracellular protein level. Collectively, ubiquitin-specific peptidases can protect LSD1 from proteasomal degradation and increase the accumulation of LSD1 by binding directly to LSD1, thereby contributing to tumorigenesis. However, the detailed underlying mechanism of LSD1 de-ubiquitination has yet to be clarified clearly (Fig. 5).

2.2.5. *KAT8-mediated acetylation*

Lysine acetyltransferase 8 (KAT8) is a member of the MYST family responsible for lysine acetyltransferases. Moreover, the acetylation modification can regulate LSD1 enzyme activity and protein stability[122]. Luo et al.[123] reported that KAT8 interacted with LSD1 to acetylate LSD1 directly at lysine 432, 433, and 436 residues in epithelial cells. Moreover, KAT8 was also required for endogenous LSD1 acetylation. This modification reduced the association of LSD1 with the nucleosome, thereby increasing the methylation of H3K4, activating transcription, and inhibiting EMT in breast cancer (Fig. 5).

2.2.6. *HDAC1-mediated deacetylation*

In addition to forming a complex with RCOR1 protein, LSD1 also exists in the histone deacetylase complex. Usually, it binds to the epigenetic enzyme HDACs that are responsible for the acetyl group's removal of acetylated lysine residues on histones or non-histones proteins. HDACs mediated the deacetylation of H3 and enhanced LSD1 activity, suggesting a close functional relationship between LSD1 and HDACs. As mentioned previously, acetylated LSD1 was identified as the cellular substrate of HDAC1 by the prior substrate trapping approach[124], and they could combine directly. Overexpressed HDAC1 was more conducive to mediating the deacetylation of LSD1 at lysine 374, which made the interaction with full-length H3 more robust. Furthermore, the methylation of H3K4me2 was inhibited, triggering increased mRNA levels of both SCN3A and SCN2A, which were associated with metastasis in prostate cancers[125] (Fig. 5). Conversely, lowering HDAC1 activity by using inhibitors or siRNA would suppress its deacetylation activity and make LSD1 acetylated at the lysine 374 site, which prompted the expression of H3K4me2[125]. Consequently, HDAC1 can enhance the demethylase function of LSD1 through deacetylation.

2.2.7. *SIRT1-mediated deacetylation*

Similar to HDAC1, SIRT1 is also an enzyme responsible for the deacetylation of proteins. Cancer-associated fibroblasts induced the direct interactions between SIRT1 and LSD1 by activating notch receptor 3 (NOTCH3) expression, thus deacetylating LSD1 to increase its stability. Therefore, enhanced LSD1 could further maintain the proliferative ability of liver cancer stem-like cells and tumor propagation *in vivo* by regulating the expression of stem cell-related transcription factors, such as SRY-Box transcription factor 2 and nanog[126] (Fig. 5). Collectively, SIRT1 can mediate the deacetylation of LSD1 and control its stability.

2.2.8. *PRMT4-mediated methylation*

LSD1 and PRMT4 coexist in the same complex, and LSD1 interacts directly with PRMT4. PRMT1, PRMT4, PRMT5, PRMT6, and PRMT7 proteins have shown methyltransferase activity against histone, but only PRMT4 catalyzes the asymmetrical dimethylation of LSD1, so LSD1 has been identified as a novel

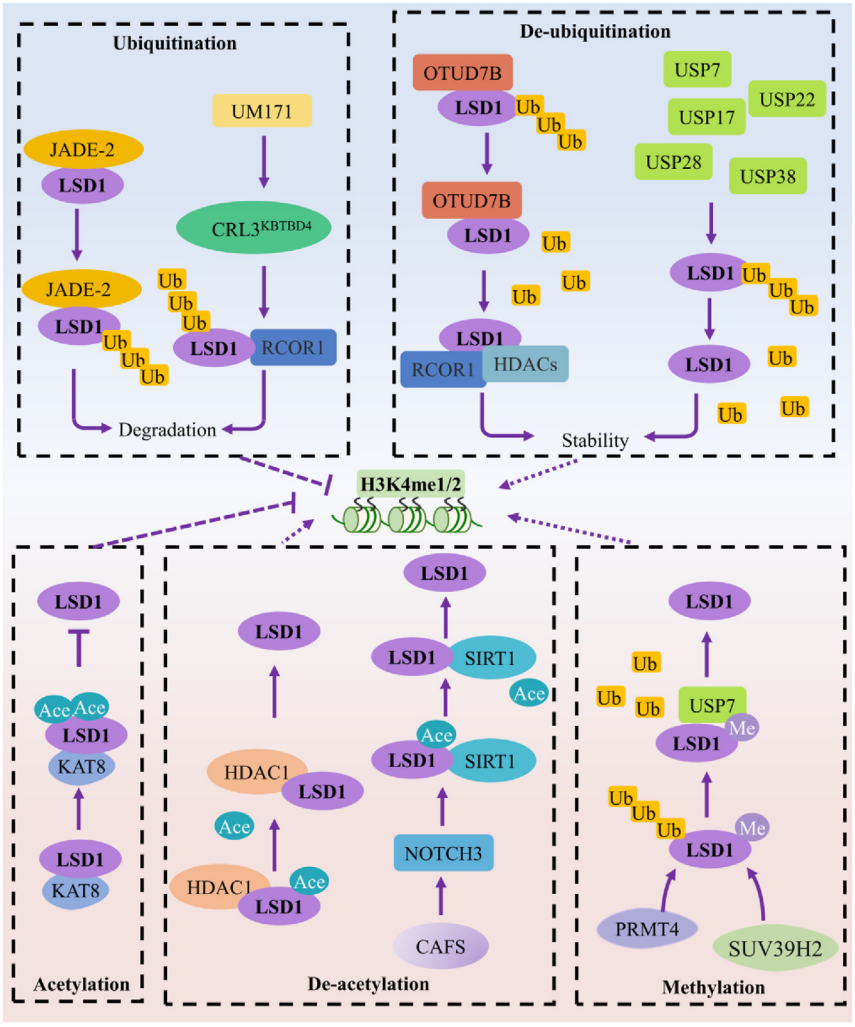

Figure 5 The working mechanism how ubiquitination enzymes JADE-2, $CRL3^{KBTBD4}$, de-ubiquitination enzymes OTUD7B and USP7/17/22/28/38, acetyltransferase KAT8, deacetylase HDAC1 or SIRT1, methyltransferase PRMT4 or SUV39H affect LSD1 activity. (1) E3 ubiquitin ligase JADE-2 binds with LSD1 directly, promoting its ubiquitination degradation, up-regulating the methylation level of H3K4me1/2; UM171 activates $CRL3^{KBTBD4}$ which targets the LSD1-RCOR1 corepressor complex and degrades LSD1. (2) OTUD7B can bind to LSD1 to eliminate the poly-Ub chains and maintain the LSD1−RCOR1−HDACs complex integrity which enhance the enzyme activity of LSD1; USP7/17/22/28/38 also eliminate the poly-Ub chains and promote the stability of LSD1. (3) KAT8 acetylates LSD1 at lysine 432, 433, and 436 residues to suppress its activity. (4) Higher HDAC1 level is conductive to deacetylate LSD1 which down-regulate the methylation level of H3K4me2; cancer-associated fibroblasts activate NOTCH3 and induce the interactions between SIRT1 and LSD1, then deacetylating LSD1 to increase its stability. (5) PRMT4 di-methylates LSD1, which promotes its binding with USP7 and deubiquitylation; SUV39H2 avoids ubiquitination degradation of LSD1 by tri-methylating LSD1.

substrate of PRMT4. PRMT4 could di-methylate LSD1 carrying the poly-Ub chains at arginine 838, which has been recognized as the only methylation site. Next, methylated LSD1 would bind to the deubiquitinating enzyme USP7, which leads to the deubiquitylation of LSD1. Moreover, the CHIP assay illuminated that the PRMT4-dependent LSD1 methylation played a dominant role in the demethylation of H3K4me2 and H3K9me2, which further caused E-cadherin gene repression and vimentin gene activation at the transcription level, thereby promoting the metastasis of breast cancer cells[127] (Fig. 5). In summary, LSD1 methylation may be more conducive to its stability.

2.2.9. *SUV39H2-mediated methylation*

Same as PRMT4, another methyltransferase SUV39H2, was previously reported to be overexpressed in non-small cell lung cancer and prostate cancer. Studies have demonstrated that SUV39H2 could tri-methylate LSD1 at lysine 322 *in vitro* and *in vivo*, which could facilitate the removal of the poly-Ub chains on LSD1 to remain LSD1 steady, further affecting LSD1-downstream genes, such as down-regulating *p21* expression and up-regulating SRY-Box transcription factor 2 expression to induce human tumor cell proliferation (Fig. 5). By contrast, loss or knockdown of SUV39H2 pronouncedly increased the polyubiquitination of LSD1 to promote its degradation, resulting in a reduced LSD1 protein level but an unchanged mRNA level[128]. This suggests that the trimethylation of LSD1 induced by SUV39H2 blocks the polyubiquitination and subsequent degradation of LSD1, thereby stabilizing LSD1.

2.2.10. *GSK3β-mediated phosphorylation*

Glycogen synthase kinase 3 (GSK3) has two subtypes (GSK3α and GSK3β)[129,130]. Emerging evidence has shown that GSK3β

plays oncogenic roles in all kinds of tumors, and GSK3β could benefit modification of H3K4 methylation in the promoter regions of bone morphogenetic protein 2 (*BMP2*) and binding protein 6 (*GATA6*)[131,132]. Under normal conditions, the stress-induced phosphoprotein 1 (STIP1) could interact with heat shock proteins 90 (HSP90)[133,134]. Afterward, the STIP1−HSP90 complex acts as a scaffold protein to promote their connection with LSD1−GSK3β, and STIP1 could then promote GSK3β-mediated phosphorylation of LSD1 (p-LSD1). Taken together, LSD1 and GSK3β interact closely with each other in the nucleus, and GSK3β-mediated p-LSD1 contributes to LSD1 retention in the nucleus, thus enhancing the stability of LSD1 protein and promoting tumor cell proliferation[135] (Fig. 6A).

Besides, it has also been reported that in human glioblastoma specimens, the protein level of LSD1 could be regulated by GSK3β in another way[82]. GSK3β catalyzes substrate phosphorylation only when a priming kinase initiates the prior phosphorylation. The kinase assays *in vitro* showed that GSK3β-mediated p-LSD1 occurred only in the presence of casein kinase 1α (CK1α). After the priming phosphorylation by CK1α at S683, GSK3β then phosphorylates LSD1 at S683. As a result, the GSK3β-dependent phosphorylation of LSD1 could induce the combination of USP22 and LSD1, thus leading to the deubiquitylation of LSD1 and enhancing its stability. Moreover, GSK3β-mediated LSD1 phosphorylation also contributed to H3K4 demethylation, thereby resulting in the suppression of LSD1 target genes such as *BMP2* and *GATA6* (Fig. 6B), further inhibiting glioma stem cells (GSCs) self-renewal and glioblastoma tumorigenesis[82]. On the contrary, when the effect of GSK3β triggered the phosphorylation of LSD1 was inhibited, LSD1 would be translocated from the nucleus to the cytoplasm, where it was degraded by 26S proteasome[135] (Fig. 6C). Taken together, GSK3β can protect LSD1 from degradation by mediating its phosphorylation.

2.2.11. *CK2 and WIP1-mediated phosphorylation*

Casein kinase 2 (CK2) can phosphorylate LSD1 at S131 and S137 sites. Conversely, wild-type p53-induced phosphatase 1 (WIP1) can induce LSD1 dephosphorylation at these two sites. LSD1 could interact with RNF168 directly, and CK2-mediated p-LSD1 would promote the physical interaction of RNF168 and LSD1. The physical interaction enabled p-LSD1 to recruit to DNA damage sites, promoting local H3K4me2 demethylation in response to DNA damage[136]. Therefore, the demethylation activity of LSD1 is enhanced by inhibiting WIP1 and increasing CK2 expression.

2.3. *Regulation of LSD1 expression by metabolites*

LSD1 was reported to be a necessary factor in altering energy metabolism and oxidative stress. Genome-wide binding and transcriptome analysis showed that LSD1 cooperated with NRF1 to directly stimulate the expression of genes associated with oxidative phosphorylation[96]. The transition from lean to fat referred to systemic metabolic remodeling that affected insulin sensitivity, lipid

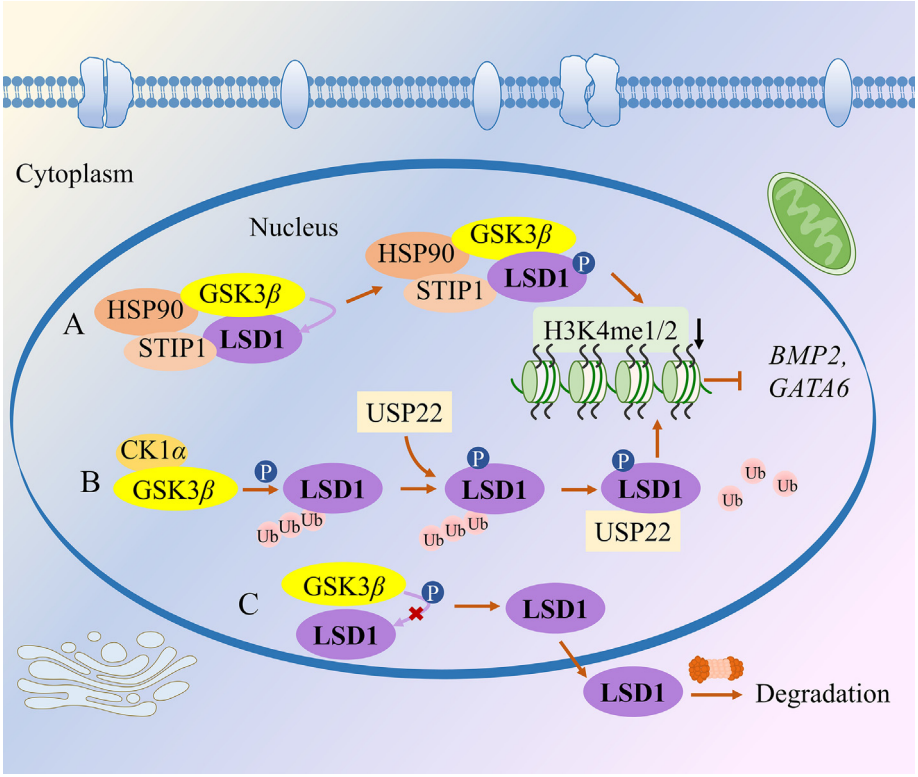

Figure 6 The roles of GSK3β in mediating LSD1 phosphorylation. (A) STIP1, HSP90, LSD1, and GSK3β interact in the nucleus. STIP1−HSP90 complex serves as a scaffold protein to forge the GSK3β-dependent phosphorylation of LSD1, which further promotes H3K4me1/2 demethylation to inhibit the expression of *BMP2* and *GATA6*. (B) CK1α initiates the phosphorylation of LSD1 in a GSK3β-dependent manner. After LSD1 is phosphorylated, it will bind to USP22 and remove Ub molecules from LSD1. Furthermore, it leads to the demethylation of H3K4me1/2, restraining target genes *BMP2* and *GATA6* expression. (C) LSD1 will be degraded after translocating from the nucleus to the cytoplasm.

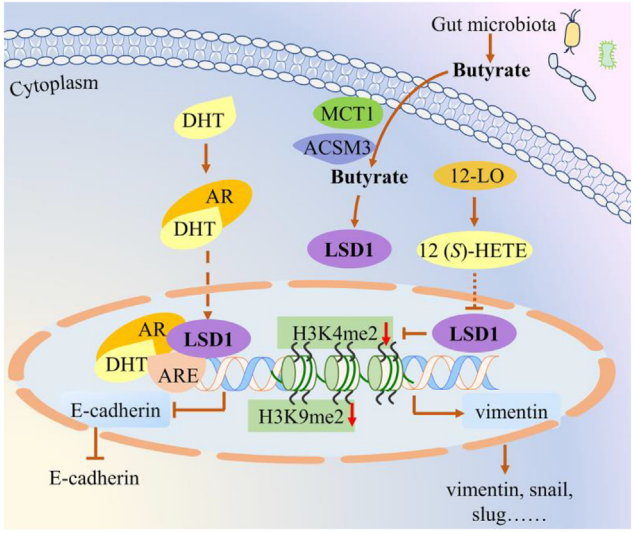

Figure 7 The effect of DHT, 12(*S*)-HETE, and butyrate on mediating LSD1 stability. (1) Androgen DHT and AR bind together to import the nucleus and recruit LSD1 to co-attach to the AREs region of the E-cadherin and vimentin promoter. By stabilizing LSD1, the expression of the E-cadherin gene is inhibited, and the vimentin gene is promoted. Taken together, it can affect related proteins in the process of EMT. (2) 12(*S*)-HETE is produced during the metabolism process of oxygenase 12-LO, which inhibits the level of the nucleus LSD1 protein. (3) Antibiotics reduce the gut microbiota, which inhibits LSD1 expression. However, with butyrate supplementation, LSD1 can be activated by MCT1 and ACSM3.

allocation, inflammation, and blood sugar control. The study has shown that administering LSD1 inhibitor GSK-LSD1 reduced food intake and body weight and improved non-alcoholic fatty liver disease, insulin sensitivity, and glycemic control in the obese mouse model. The finding suggested that targeting LSD1 may be a viable strategy for regulating obesity-related metabolic reprogramming[137]. In contrast, metabolites in oxidative metabolism or other metabolic processes, such as DHT, 12(*S*)-HETE, and butyrate, also regulated LSD1 expression. In the following part, we will describe how some metabolites affect the LSD1 levels.

2.3.1. *Androgen dihydrotestosterone (DHT)*

Androgens were found in males and detected in the circulation of women[138]. Most studies have shown a positive association between female breast cancer risk and high levels of androgens and androgen receptor (AR)-mediated biological effects of androgens[139,140]. Epithelioid Erα^{-}/AR^{+} cell line T47D was treated with DHT, and the results showed that DHT induced EMT in an AR-dependent/ERα-independent manner. Under DHT stimulation, AR was first induced to occur nuclear translocation and activated the demethylation activity of LSD1, resulting in the binding of AR and LSD1 to the AREs regions of E-cadherin and vimentin promoters. AR and LSD1 were found to be enriched in the promoter region of E-cadherin. This enrichment was accompanied by a decrease in the active chromatin marker H3K4me2, as well as a slight increase in the repressive chromatin marker H3K9me2. These changes ultimately led to the inhibition of E-cadherin gene expression. In addition, DHT stimulation increased the enrichment of AR and LSD1 in the vimentin promoter, significantly decreased H3K9me2, and moderately increased H3K4me2, promoting the expression of the vimentin gene. Therefore, AR and LSD1 synergically inhibited E-cadherin promoter activity and enhanced vimentin promoter activity and these two genes were essential target genes in the process of EMT. Moreover, other EMT inducers, such as snail, slug, and zearalenone biosynthesis protein 1/2, were detected to be up-regulated[141] (Fig. 7). In conclusion, AR enters the nucleus and recruits LSD1 to regulate target genes E-cadherin and vimentin through epigenetic regulation, leading to the EMT process, thus promoting breast cancer metastasis.

2.3.2. *12(S)-HETE*

12(*S*)-Hydroxy eicosatetraenoic acid [12(*S*)-HETE] is a metabolite of 12-lipoxygenase (12-LO)[142]. 12(*S*)-HETE induced the methylation modification of H3K4 by reducing the nuclear protein level of LSD1 through CHIP assays and Western blot analysis of nuclear protein lysates extracted from rat mesangial cells[143] (Fig. 7). However, the detailed mechanism needs to be further explored.

2.3.3. *Butyrate*

The gut microbiota and its metabolite, butyrate, have been shown to regulate energy production and potentially improve metabolic health[144]. Depletion of gut microbiota by antibiotics disrupted the thermogenic cycle in mice, and LSD1 expression was decreased. However, butyrate supplementation in antibiotic-treated mice promoted the expression of LSD1. Furthermore, the study on adipocyte culture *in vitro* also showed that butyrate could pass through monocarboxylate transporter 1 (MCT1) and acyl-CoA medium-chain synthetase 3 (ACSM3) to activate LSD1 and directly induce adipocyte to generate heat. Although it was confirmed that gut microbiota and butyrate straightforwardly up-regulated LSD1 expression and induced heat production in an AMPK-independent manner, the mechanism by which butyrate activated LSD1 remains unclear[145] (Fig. 7).

3. Conclusions and perspectives

Since its first discovery in 2004[146], LSD1 has been reported to be essential in some normal biological processes and human diseases, including cancers[38]. As an oncogene, *LSD1* is overexpressed in many cancers[147]. And so far, many highly potent and selective LSD1 inhibitors have been reported, including natural products, peptides, and synthetic compounds. Among them, Tranylcypromine, ORY-1001, GSK2879552, INCB059872, IMG-7289, and CC-90011 have entered different stages of clinical evaluation for cancer treatment[51]. In addition, small-molecule BEA-17, through binding to the allosteric site, can down-regulate LSD1 expression without directly inhibiting its enzyme function. BEA-17 inhibits the initial clones by reducing nuclear LSD1 levels in glioblastoma[148]. BEA-17 can also up-regulate the expression of endogenous retrovirus genes and T cells-inducing chemokines in an LSD1-dependent manner, enhancing immunotherapy. In the co-culture of HeLa and peripheral blood mononuclear cells (PBMCs), BEA-17 increases the killing of cancer cells by immune effector T cells in an LSD1-dependent manner[149]. These small molecule inhibitors can inhibit the differentiation, proliferation, invasion, and migration or promote immune response in cancer cells. LSD1 is an emerging target for anticancer therapy. Strategies for developing LSD1 inhibitors by targeting its protein levels or enzyme activity are well-established, leading to the discovery of numerous LSD1 inhibitors. However, certain LSD1 inhibitors have exhibited toxicity in clinical trials.

LSD1 is subject to dynamic regulation, with certain interacting proteins to form the LSD1 corepressor complex. Among these proteins are RCOR1, BHC80, and HADC1, which could influence the function of LSD1. In this review, we elucidated how these proteins impact the activity of LSD1. In addition, we all know that the protein level is usually balanced under the regulatory effect of some ubiquitinating enzymes, deubiquitinating enzymes, methyltransferases, acetylases, deacetylases, and phosphorylases. Next, we highlighted the impact of these enzymes on LSD1 protein levels. It is worth noting that certain metabolites can also influence the stability of epigenetic enzymes. In this review, we stated how DHT, butyrate, and 12(*S*)-HETE affect LSD1 expression.

Most importantly, as a selective HDAC inhibitor, 4SC-202 selectively inhibits class I HDAC isoenzymes such as HDAC1, HDAC2, and HDAC3[150]. Interestingly, 4SC-202 also has an excellent potency in inhibiting LSD1 in current clinical trials[151]. Therefore, we suspect that small molecule inhibitors targeting other proteins could potentially inhibit LSD1 and directly affect its demethylation function. This opens up a new avenue for developing inhibitors by modulating the stability of proteins that interact with LSD1 or certain metabolites. This review has listed the factors that regulate LSD1 function and provides a basis for developing inhibitors that target these factors.

Acknowledgments

This work was supported by Natural Science Foundation of China (Nos. 81903770, 81973177, and 22277110, China), Joint Funds of Technology Research and Development Plan of Henan Province (No. 232301420058, China), China Postdoctoral Science Foundation (No. 2019M662556, China), Key scientific and technological projects of Henan Province (No. 222102310125, China), Natural Science Foundation of Henan Province (No. 222300420069, China), Program for Science & Technology Innovation Talents in Universities of Henan Province (No. 21HASTIT045, China), Cultivation Project of Zhengzhou University (JC23852097, China), Tianjian Laboratory of Advanced Biomedical Sciences, and the open fund of State Key Laboratory of Pharmaceutical Biotechnology, Nanjing University, China (No. KF-202303, China).

Author contributions

Meng Li: Data Processing, Writing-Original Draft, Writing-Review & Editing. Mengge Dai: Figures Making, Visualization, Investigation. Bing Cheng: Visualization, Investigation. Shaotong Li: Visualization, Investigation. Enhui Guo: Visualization. Junwei Fu: Investigation. Ting Ma: Project administration, Funding acquisition, Modification, Supervision. Bin Yu: Manuscript revision, Funding acquisition, Supervision.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Maris JM, Matthay KK. Molecular biology of neuroblastoma. *J Clin Oncol* 1999;**17**:2264−79.
2. Hogg SJ, Beavis PA, Dawson MA, Johnstone RW. Targeting the epigenetic regulation of antitumour immunity. *Nat Rev Drug Discov* 2020;**19**:776−800.
3. Dawson MA, Kouzarides T. Cancer epigenetics: from mechanism to therapy. *Cell* 2012;**150**:12−27.
4. Shi Y, Whetstine JR. Dynamic regulation of histone lysine methylation by demethylases. *Mol Cell* 2007;**25**:1−14.
5. Mimasu S, Sengoku T, Fukuzawa S, Umehara T, Yokoyama S. Crystal structure of histone demethylase LSD1 and tranylcypromine at 2.25 A. *Biochem Biophys Res Commun* 2008;**366**:15−22.
6. Yang M, Culhane JC, Szewczuk LM, Gocke CB, Brautigam CA, Tomchick DR, et al. Structural basis of histone demethylation by LSD1 revealed by suicide inactivation. *Nat Struct Mol Biol* 2007;**14**:535−9.
7. Metzger E, Wissmann M, Yin N, Müller JM, Schneider R, Peters AH, et al. LSD1 demethylates repressive histone marks to promote androgen-receptor-dependent transcription. *Nature* 2005;**437**:436−9.
8. Wissmann M, Yin N, Müller JM, Greschik H, Fodor BD, Jenuwein T, et al. Cooperative demethylation by JMJD2C and LSD1 promotes androgen receptor-dependent gene expression. *Nat Cell Biol* 2007;**9**:347−53.
9. Perillo B, Ombra MN, Bertoni A, Cuozzo C, Sacchetti S, Sasso A, et al. DNA oxidation as triggered by H3K9me2 demethylation drives estrogen-induced gene expression. *Science* 2008;**319**:202−6.
10. Maiques-Diaz A, Somervaille TC. LSD1: biologic roles and therapeutic targeting. *Epigenomics* 2016;**8**:1103−16.
11. Amente S, Bertoni A, Morano A, Lania L, Avvedimento EV, Majello B. LSD1-mediated demethylation of histone H3 lysine 4 triggers Myc-induced transcription. *Oncogene* 2010;**29**:3691−702.
12. Garcia-Bassets I, Kwon YS, Telese F, Prefontaine GG, Hutt KR, Cheng CS, et al. Histone methylation-dependent mechanisms impose ligand dependency for gene activation by nuclear receptors. *Cell* 2007;**128**:505−18.
13. Metzger E, Imhof A, Patel D, Kahl P, Hoffmeyer K, Friedrichs N, et al. Phosphorylation of histone H3T6 by PKCbeta(I) controls demethylation at histone H3K4. *Nature* 2010;**464**:792−6.
14. Nair SS, Nair BC, Cortez V, Chakravarty D, Metzger E, Schüle R, et al. PELP1 is a reader of histone H3 methylation that facilitates oestrogen receptor-alpha target gene activation by regulating lysine demethylase 1 specificity. *EMBO Rep* 2010;**11**:438−44.
15. Lee MG, Wynder C, Cooch N, Shiekhattar R. An essential role for CoREST in nucleosomal histone 3 lysine 4 demethylation. *Nature* 2005;**437**:432−5.
16. Kim D, Kim KI, Baek SH. Roles of lysine-specific demethylase 1 (LSD1) in homeostasis and diseases. *J Biomed Sci* 2021;**28**:41.
17. Gu F, Lin Y, Wang Z, Wu X, Ye Z, Wang Y, et al. Biological roles of LSD1 beyond its demethylase activity. *Cell Mol Life Sci* 2020;**77**:3341−50.
18. Martinez-Gamero C, Malla S, Aguilo F. LSD1: expanding functions in stem cells and differentiation. *Cells* 2021;**10**:3252.
19. Gao S, Chen S, Han D, Wang Z, Li M, Han W, et al. Chromatin binding of FOXA1 is promoted by LSD1-mediated demethylation in prostate cancer. *Nat Genet* 2020;**52**:1011−7.
20. Harancher MR, Packard JE, Cowan SP, DeLuca NA, Dembowski JA. Antiviral properties of the LSD1 inhibitor SP-2509. *J Virol* 2020;**94**:e00974-20.
21. Yang J, Huang J, Dasgupta M, Sears N, Miyagi M, Wang B, et al. Reversible methylation of promoter-bound STAT3 by histone-modifying enzymes. *Proc Natl Acad Sci U S A* 2010;**107**:21499−504.
22. Huang J, Sengupta R, Espejo AB, Lee MG, Dorsey JA, Richter M, et al. p53 is regulated by the lysine demethylase LSD1. *Nature* 2007;**449**:105−8.
23. Scoumanne A, Chen X. The lysine-specific demethylase 1 is required for cell proliferation in both p53-dependent and -independent manners. *J Biol Chem* 2007;**282**:15471−5.
24. Kontaki H, Talianidis I. Lysine methylation regulates E2F1-induced cell death. *Mol Cell* 2010;**39**:152−60.
25. Sheng W, LaFleur MW, Nguyen TH, Chen S, Chakravarthy A, Conway JR, et al. LSD1 ablation stimulates anti-tumor immunity and enables checkpoint blockade. *Cell* 2018;**174**:549−563.e19.

26. Cho HS, Suzuki T, Dohmae N, Hayami S, Unoki M, Yoshimatsu M, et al. Demethylation of RB regulator MYPT1 by histone demethylase LSD1 promotes cell cycle progression in cancer cells. *Cancer Res* 2011;**71**:655−60.
27. Nair SS, Li DQ, Kumar R. A core chromatin remodeling factor instructs global chromatin signaling through multivalent reading of nucleosome codes. *Mol Cell* 2013;**49**:704−18.
28. Lee JY, Park JH, Choi HJ, Won HY, Joo HS, Shin DH, et al. LSD1 demethylates HIF1α to inhibit hydroxylation and ubiquitin-mediated degradation in tumor angiogenesis. *Oncogene* 2017;**36**:5512−21.
29. Kim Y, Nam HJ, Lee J, Park DY, Kim C, Yu YS, et al. Methylation-dependent regulation of HIF-1α stability restricts retinal and tumour angiogenesis. *Nat Commun* 2016;**7**:10347.
30. Bao L, Chen Y, Lai HT, Wu SY, Wang JE, Hatanpaa KJ, et al. Methylation of hypoxia-inducible factor (HIF)-1α by G9a/GLP inhibits HIF-1 transcriptional activity and cell migration. *Nucleic Acids Res* 2018;**46**:6576−91.
31. Fang Y, Yang C, Yu Z, Li X, Mu Q, Liao G, et al. Natural products as LSD1 inhibitors for cancer therapy. *Acta Pharm Sin B* 2020;**11**:621−31.
32. Amente S, Lania L, Majello B. The histone LSD1 demethylase in stemness and cancer transcription programs. *Biochim Biophys Acta* 2013;**1829**:981−6.
33. Majello B, Gorini F, Saccà CD, Amente S. Expanding the role of the histone lysine-specific demethylase LSD1 in cancer. *Cancers* 2019;**11**:324.
34. Hill JM, Quenelle DC, Cardin RD, Vogel JL, Clement C, Bravo FJ, et al. Inhibition of LSD1 reduces herpesvirus infection, shedding, and recurrence by promoting epigenetic suppression of viral genomes. *Sci Transl Med* 2014;**6**:265ra169.
35. Qin Y, Vasilatos SN, Chen L, Wu H, Cao Z, Fu Y, et al. Inhibition of histone lysine-specific demethylase 1 elicits breast tumor immunity and enhances antitumor efficacy of immune checkpoint blockade. *Oncogene* 2019;**38**:390−405.
36. Hatzi K, Geng H, Doane AS, Meydan C, LaRiviere R, Cardenas M, et al. Histone demethylase LSD1 is required for germinal center formation and BCL6-driven lymphomagenesis. *Nat Immunol* 2019;**20**:86−96.
37. Zhu L, Wang J, Kong W, Huang J, Dong B, Huang Y, et al. LSD1 inhibition suppresses the growth of clear cell renal cell carcinoma *via* upregulating P21 signaling. *Acta Pharm Sin B* 2019;**9**:324−34.
38. Shen DD, Pang JR, Bi YP, Zhao LF, Li YR, Zhao LJ, et al. LSD1 deletion decreases exosomal PD-L1 and restores T-cell response in gastric cancer. *Mol Cancer* 2022;**21**:75.
39. Abdel-Magid AF. Lysine-specific demethylase 1 (LSD1) inhibitors as potential treatment for different types of cancers. *ACS Med Chem Lett* 2017;**8**:1134−5.
40. Xu S, Wang X, Yang Y, Li Y, Wu S. LSD1 silencing contributes to enhanced efficacy of anti-CD47/PD-L1 immunotherapy in cervical cancer. *Cell Death Dis* 2021;**12**:282.
41. Vinyard ME, Su C, Siegenfeld AP, Waterbury AL, Freedy AM, Gosavi PM, et al. CRISPR-suppressor scanning reveals a nonenzymatic role of LSD1 in AML. *Nat Chem Biol* 2019;**15**:529−39.
42. Zhang S, Liu M, Yao Y, Yu B, Liu H. Targeting LSD1 for acute myeloid leukemia (AML) treatment. *Pharmacol Res* 2021;**164**:105335.
43. Feng J, Xu G, Liu J, Zhang N, Li L, Ji J, et al. Phosphorylation of LSD1 at Ser112 is crucial for its function in induction of EMT and metastasis in breast cancer. *Breast Cancer Res Treat* 2016;**159**:443−56.
44. Sugino N, Kawahara M, Tatsumi G, Kanai A, Matsui H, Yamamoto R, et al. A novel LSD1 inhibitor NCD38 ameliorates MDS-related leukemia with complex karyotype by attenuating leukemia programs *via* activating super-enhancers. *Leukemia* 2017;**31**:2303−14.
45. Dai XJ, Liu Y, Xue LP, Xiong XP, Zhou Y, Zheng YC, et al. Reversible lysine specific demethylase 1 (LSD1) inhibitors: a promising wrench to impair LSD1. *J Med Chem* 2021;**64**:2466−88.
46. Ota Y, Suzuki T. Drug design concepts for LSD1-selective inhibitors. *Chem Rec* 2018;**18**:1782−91.
47. Fu DJ, Li J, Yu B. Annual review of LSD1/KDM1A inhibitors in 2020. *Eur J Med Chem* 2021;**214**:113254.
48. Song Y, Zhang H, Yang X, Shi Y, Yu B. Annual review of lysine-specific demethylase 1 (LSD1/KDM1A) inhibitors in 2021. *Eur J Med Chem* 2022;**228**:114042.
49. Lv YX, Tian S, Zhang ZD, Feng T, Li HQ. LSD1 inhibitors for anticancer therapy: a patent review (2017−present). *Expert Opin Ther Pat* 2022;**32**:1027−42.
50. Dai XJ, Zhao LJ, Yang LH, Guo T, Xue LP, Ren HM, et al. Phenothiazine-based LSD1 inhibitor promotes T-cell killing response of gastric cancer cells. *J Med Chem* 2023;**66**:3896−916.
51. Fang Y, Liao G, Yu B. LSD1/KDM1A inhibitors in clinical trials: advances and prospects. *J Hematol Oncol* 2019;**12**:129.
52. Song Y, Yang X, Yu B. Repurposing antidepressants for anticancer drug discovery. *Drug Discov Today* 2022;**27**:1924−35.
53. Maes T, Mascaró C, Tirapu I, Estiarte A, Ciceri F, Lunardi S, et al. ORY-1001, a potent and selective covalent KDM1A inhibitor, for the treatment of acute leukemia. *Cancer Cell* 2018;**33**:495−511.e12.
54. Salamero O, Montesinos P, Willekens C, Pérez-Simón JA, Pigneux A, Récher C, et al. First-in-human phase i study of iadademstat (ORY-1001): a first-in-class lysine-specific histone demethylase 1A inhibitor, in relapsed or refractory acute myeloid leukemia. *J Clin Oncol* 2020;**38**:4260−73.
55. Maes T, Mascaró C, Rotllant D, Lufino MMP, Estiarte A, Guibourt N, et al. Modulation of KDM1A with vafidemstat rescues memory deficit and behavioral alterations. *PLoS One* 2020;**15**:e0233468.
56. Mohammad HP, Smitheman KN, Kamat CD, Soong D, Federowicz KE, Van Aller GS, et al. A DNA hypomethylation signature predicts antitumor activity of LSD1 inhibitors in SCLC. *Cancer Cell* 2015;**28**:57−69.
57. Li C, Su M, Zhu W, Kan W, Ge T, Xu G, et al. Structure−activity relationship study of indolin-5-yl-cyclopropanamine derivatives as selective lysine specific demethylase 1 (LSD1) inhibitors. *J Med Chem* 2022;**65**:4335−49.
58. Kanouni T, Severin C, Cho RW, Yuen NY, Xu J, Shi L, et al. Discovery of CC-90011: a potent and selective reversible inhibitor of lysine specific demethylase 1 (LSD1). *J Med Chem* 2020;**63**:14522−9.
59. Zhang C, Wang Z, Shi Y, Yu B, Song Y. Recent advances of LSD1/KDM1A inhibitors for disease therapy. *Bioorg Chem* 2023;**134**:106443.
60. Wang Y, Huang Y, Cheng E, Liu X, Zhang Y, Yang J, et al. LSD1 is required for euchromatic origin firing and replication timing. *Signal Transduct Targeted Ther* 2022;**7**:102.
61. Witt O, Deubzer HE, Milde T, Oehme I. HDAC family: what are the cancer relevant targets?. *Cancer Lett* 2009;**277**:8−21.
62. Yao H, Goldman DC, Nechiporuk T, Kawane S, McWeeney SK, Tyner JW, et al. Corepressor Rcor1 is essential for murine erythropoiesis. *Blood* 2014;**123**:3175−84.
63. Shi YJ, Matson C, Lan F, Iwase S, Baba T, Shi Y. Regulation of LSD1 histone demethylase activity by its associated factors. *Mol Cell* 2005;**19**:857−64.
64. Esteghamat F, van Dijk TB, Braun H, Dekker S, van der Linden R, Hou J, et al. The DNA binding factor Hmg20b is a repressor of erythroid differentiation. *Haematologica* 2011;**96**:1252−60.
65. Vendrell JA, Thollet A, Nguyen NT, Ghayad SE, Vinot S, Bièche I, et al. ZNF217 is a marker of poor prognosis in breast cancer that drives epithelial−mesenchymal transition and invasion. *Cancer Res* 2012;**72**:3593−606.
66. Banck MS, Li S, Nishio H, Wang C, Beutler AS, Walsh MJ. The ZNF217 oncogene is a candidate organizer of repressive histone modifiers. *Epigenetics* 2009;**4**:100−6.
67. Si W, Zhao Y, Zhou J, Zhang Q, Zhang Y. The coordination between ZNF217 and LSD1 contributes to hepatocellular carcinoma progress

and is negatively regulated by miR-101. *Exp Cell Res* 2019;**379**:1−10.
68. Coni S, Serrao SM, Yurtsever ZN, Di Magno L, Bordone R, Bertani C, et al. Blockade of EIF5A hypusination limits colorectal cancer growth by inhibiting MYC elongation. *Cell Death Dis* 2020;**11**:1045.
69. Wolff EC, Lee YB, Chung SI, Folk JE, Park MH. Deoxyhypusine synthase from rat testis: purification and characterization. *J Biol Chem* 1995;**270**:8660−6.
70. Park MH, Cooper HL, Folk JE. Identification of hypusine, an unusual amino acid, in a protein from human lymphocytes and of spermidine as its biosynthetic precursor. *Proc Natl Acad Sci U S A* 1981;**78**:2869−73.
71. Li H, Wu BK, Kanchwala M, Cai J, Wang L, Xing C, et al. YAP/TAZ drives cell proliferation and tumour growth *via* a polyamine−eIF5A hypusination−LSD1 axis. *Nat Cell Biol* 2022;**24**:373−83.
72. Lan F, Collins RE, De Cegli R, Alpatov R, Horton JR, Shi X, et al. Recognition of unmethylated histone H3 lysine 4 links BHC80 to LSD1-mediated gene repression. *Nature* 2007;**448**:718−22.
73. Mulligan P, Westbrook TF, Ottinger M, Pavlova N, Chang B, Macia E, et al. CDYL bridges REST and histone methyltransferases for gene repression and suppression of cellular transformation. *Mol Cell* 2008;**32**:718−26.
74. Ouyang J, Shi Y, Valin A, Xuan Y, Gill G. Direct binding of CoREST1 to SUMO-2/3 contributes to gene-specific repression by the LSD1/CoREST1/HDAC complex. *Mol Cell* 2009;**34**:145−54.
75. Kim SA, Zhu J, Yennawar N, Eek P, Tan S. Crystal structure of the LSD1/CoREST histone demethylase bound to its nucleosome substrate. *Mol Cell* 2020;**78**:903−914.e4.
76. Yang M, Gocke CB, Luo X, Borek D, Tomchick DR, Machius M, et al. Structural basis for CoREST-dependent demethylation of nucleosomes by the human LSD1 histone demethylase. *Mol Cell* 2006;**23**:377−87.
77. Chen Y, Yang Y, Wang F, Wan K, Yamane K, Zhang Y, et al. Crystal structure of human histone lysine-specific demethylase 1 (LSD1). *Proc Natl Acad Sci U S A* 2006;**103**:13956−61.
78. Stavropoulos P, Blobel G, Hoelz A. Crystal structure and mechanism of human lysine-specific demethylase-1. *Nat Struct Mol Biol* 2006;**13**:626−32.
79. Hwang S, Schmitt AA, Luteran AE, Toone EJ, McCafferty DG. Thermodynamic characterization of the binding interaction between the histone demethylase LSD1/KDM1 and CoREST. *Biochemistry* 2011;**50**:546−57.
80. Tao M, Liu T, You Q, Jiang Z. p62 as a therapeutic target for tumor. *Eur J Med Chem* 2020;**193**:112231.
81. Babu JR, Geetha T, Wooten MW. Sequestosome 1/p62 shuttles polyubiquitinated tau for proteasomal degradation. *J Neurochem* 2005;**94**:192−203.
82. Zhou A, Lin K, Zhang S, Chen Y, Zhang N, Xue J, et al. Nuclear GSK3β promotes tumorigenesis by phosphorylating KDM1A and inducing its deubiquitylation by USP22. *Nat Cell Biol* 2016;**18**:954−66.
83. Welchman RL, Gordon C, Mayer RJ. Ubiquitin and ubiquitin-like proteins as multifunctional signals. *Nat Rev Mol Cell Biol* 2005;**6**:599−609.
84. Gong Z, Li A, Ding J, Li Q, Zhang L, Li Y, et al. OTUD7B deubiquitinates LSD1 to govern its binding partner specificity, homeostasis, and breast cancer metastasis. *Adv Sci* 2021;**8**:e2004504.
85. Lin CY, Chang CB, Wu RC, Chao A, Lee YS, Tsai CN, et al. Glucose activates lysine-specific demethylase 1 through the KEAP1/p62 pathway. *Antioxidants* 2021;**10**:1898.
86. Jaramillo MC, Zhang DD. The emerging role of the Nrf2−Keap1 signaling pathway in cancer. *Genes Dev* 2013;**27**:2179−91.
87. Suzuki T, Yamamoto M. Molecular basis of the Keap1−Nrf2 system. *Free Radic Biol Med* 2015;**88**:93−100.
88. Tsai WW, Nguyen TT, Shi Y, Barton MC. p53-targeted LSD1 functions in repression of chromatin structure and transcription *in vivo*. *Mol Cell Biol* 2008;**28**:5139−46.
89. Nicholson TB, Chen T. LSD1 demethylates histone and non-histone proteins. *Epigenetics* 2009;**4**:129−32.
90. Battaglioni S, Benjamin D, Wälchli M, Maier T, Hall MN. mTOR substrate phosphorylation in growth control. *Cell* 2022;**185**:1814−36.
91. Doi K, Murata K, Ito S, Suzuki A, Terao C, Ishie S, et al. Role of lysine-specific demethylase 1 in metabolically integrating osteoclast differentiation and inflammatory bone resorption through hypoxia-inducible factor 1α and E2F1. *Arthritis Rheumatol* 2022;**74**:948−60.
92. Masoud GN, Li W. HIF-1α pathway: role, regulation and intervention for cancer therapy. *Acta Pharm Sin B* 2015;**5**:378−89.
93. Chang CC, Lin BR, Chen ST, Hsieh TH, Li YJ, Kuo MY. HDAC2 promotes cell migration/invasion abilities through HIF-1α stabilization in human oral squamous cell carcinoma. *J Oral Pathol Med* 2011;**40**:567−75.
94. Qin Y, Zhu W, Xu W, Zhang B, Shi S, Ji S, et al. LSD1 sustains pancreatic cancer growth *via* maintaining HIF1α-dependent glycolytic process. *Cancer Lett* 2014;**347**:225−32.
95. Lee K, Kitagawa M, Liao PJ, Virshup DM, Lee SH. A Ras−LSD1 axis activates PI3K signaling through PIK3IP1 suppression. *Oncogenesis* 2020;**9**:2.
96. Duteil D, Metzger E, Willmann D, Karagianni P, Friedrichs N, Greschik H, et al. LSD1 promotes oxidative metabolism of white adipose tissue. *Nat Commun* 2014;**5**:4093.
97. Carnesecchi J, Forcet C, Zhang L, Tribollet V, Barenton B, Boudra R, et al. ERRα induces H3K9 demethylation by LSD1 to promote cell invasion. *Proc Natl Acad Sci U S A* 2017;**114**:3909−14.
98. Zhang H, Xing J, Zhao L. Lysine-specific demethylase 1 induced epithelial−mesenchymal transition and promoted renal fibrosis through Jagged-1/Notch signaling pathway. *Hum Exp Toxicol* 2021;**40**:S203−14.
99. Chen RH, Chen YH, Huang TY. Ubiquitin-mediated regulation of autophagy. *J Biomed Sci* 2019;**26**:80.
100. Shang F, Taylor A. Ubiquitin−proteasome pathway and cellular responses to oxidative stress. *Free Radic Biol Med* 2011;**51**:5−16.
101. Barghout SH, Schimmer AD. E1 enzymes as therapeutic targets in cancer. *Pharmacol Rev* 2021;**73**:1−58.
102. Asmamaw MD, Liu Y, Zheng YC, Shi XJ, Liu HM. Skp2 in the ubiquitin-proteasome system: a comprehensive review. *Med Res Rev* 2020;**40**:1920−49.
103. Song Q, Feng S, Peng W, Li A, Ma T, Yu B, et al. Cullin−RING ligases as promising targets for gastric carcinoma treatment. *Pharmacol Res* 2021;**170**:105493.
104. Sun T, Liu Z, Yang Q. The role of ubiquitination and deubiquitination in cancer metabolism. *Mol Cancer* 2020;**19**:146.
105. Park HB, Kim JW, Baek KH. Regulation of Wnt signaling through ubiquitination and deubiquitination in cancers. *Int J Mol Sci* 2020;**21**:3904.
106. Han X, Gui B, Xiong C, Zhao L, Liang J, Sun L, et al. Destabilizing LSD1 by Jade-2 promotes neurogenesis: an antibraking system in neural development. *Mol Cell* 2014;**55**:482−94.
107. Chagraoui J, Girard S, Spinella JF, Simon L, Bonneil E, Mayotte N, et al. UM171 preserves epigenetic marks that are reduced in *ex vivo* culture of human HSCs *via* potentiation of the CLR3−KBTBD4 complex. *Cell Stem Cell* 2021;**28**:48−62.e6.
108. Liu W, Zhang Q, Fang Y, Wang Y. The deubiquitinase USP38 affects cellular functions by interacting with LSD1. *Biol Res* 2018;**51**:53.
109. Liu W, Wang D, Liu L, Wang L, Yan M. miR-140 inhibits osteosarcoma progression by impairing USP22-mediated LSD1 stabilization and promoting p21 expression. *Mol Ther Nucleic Acids* 2021;**24**:436−48.
110. Yi L, Cui Y, Xu Q, Jiang Y. Stabilization of LSD1 by deubiquitinating enzyme USP7 promotes glioblastoma cell tumorigenesis and metastasis through suppression of the p53 signaling pathway. *Oncol Rep* 2016;**36**:2935−45.
111. Wu Y, Wang Y, Yang XH, Kang T, Zhao Y, Wang C, et al. The deubiquitinase USP28 stabilizes LSD1 and confers stem-cell-like traits to breast cancer cells. *Cell Rep* 2013;**5**:224−36.

112. Shvedunova M, Akhtar A. Modulation of cellular processes by histone and non-histone protein acetylation. *Nat Rev Mol Cell Biol* 2022;**23**:329−49.
113. Shen Y, Wei W, Zhou DX. Histone acetylation enzymes coordinate metabolism and gene expression. *Trends Plant Sci* 2015;**20**:614−21.
114. Wang P, Wang Z, Liu J. Role of HDACs in normal and malignant hematopoiesis. *Mol Cancer* 2020;**19**:5.
115. Anan K, Hino S, Shimizu N, Sakamoto A, Nagaoka K, Takase R, et al. LSD1 mediates metabolic reprogramming by glucocorticoids during myogenic differentiation. *Nucleic Acids Res* 2018;**46**:5441−54.
116. Fares I, Chagraoui J, Gareau Y, Gingras S, Ruel R, Mayotte N, et al. Cord blood expansion. Pyrimidoindole derivatives are agonists of human hematopoietic stem cell self-renewal. *Science* 2014;**345**:1509−12.
117. Subramaniam A, Žemaitis K, Talkhoncheh MS, Yudovich D, Bäckström A, Debnath S, et al. Lysine-specific demethylase 1A restricts *ex vivo* propagation of human HSCs and is a target of UM171. *Blood* 2020;**136**:2151−61.
118. Bonacci T, Emanuele MJ. Dissenting degradation: deubiquitinases in cell cycle and cancer. *Semin Cancer Biol* 2020;**67**:145−58.
119. Bhattacharya S, Chakraborty D, Basu M, Ghosh MK. Emerging insights into HAUSP (USP7) in physiology, cancer and other diseases. *Signal Transduct Targeted Ther* 2018;**3**:17.
120. Ling S, Shan Q, Zhan Q, Ye Q, Liu P, Xu S, et al. USP22 promotes hypoxia-induced hepatocellular carcinoma stemness by a HIF1α/USP22 positive feedback loop upon TP53 inactivation. *Gut* 2020;**69**:1322−34.
121. Liu Z, Zhao T, Li Z, Sun K, Fu Y, Cheng T, et al. Discovery of [1,2,3]triazolo[4,5-*d*]pyrimidine derivatives as highly potent, selective, and cellularly active USP28 inhibitors. *Acta Pharm Sin B* 2020;**10**:1476−91.
122. Horikoshi N, Hunt CR, Pandita TK. More complex transcriptional regulation and stress response by MOF. *Oncogene* 2016;**35**:2681−3.
123. Luo H, Shenoy AK, Li X, Jin Y, Jin L, Cai Q, et al. MOF acetylates the histone demethylase LSD1 to suppress epithelial-to-mesenchymal transition. *Cell Rep* 2016;**15**:2665−78.
124. Flint AJ, Tiganis T, Barford D, Tonks NK. Development of "substrate-trapping" mutants to identify physiological substrates of protein tyrosine phosphatases. *Proc Natl Acad Sci U S A* 1997;**94**:1680−5.
125. Nalawansha DA, Pflum MK. LSD1 substrate binding and gene expression are affected by HDAC1-mediated deacetylation. *ACS Chem Biol* 2017;**12**:254−64.
126. Liu C, Liu L, Chen X, Cheng J, Zhang H, Zhang C, et al. LSD1 stimulates cancer-associated fibroblasts to drive Notch3-dependent self-renewal of liver cancer stem-like cells. *Cancer Res* 2018;**78**:938−49.
127. Liu J, Feng J, Li L, Lin L, Ji J, Lin C, et al. Arginine methylation-dependent LSD1 stability promotes invasion and metastasis of breast cancer. *EMBO Rep* 2020;**21**:e48597.
128. Piao L, Suzuki T, Dohmae N, Nakamura Y, Hamamoto R. SUV39H2 methylates and stabilizes LSD1 by inhibiting polyubiquitination in human cancer cells. *Oncotarget* 2015;**6**:16939−50.
129. Cohen P, Frame S. The renaissance of GSK3. *Nat Rev Mol Cell Biol* 2001;**2**:769−76.
130. Doble BW, Woodgett JR. GSK-3: tricks of the trade for a multitasking kinase. *J Cell Sci* 2003;**116**:1175−86.
131. Ougolkov AV, Bone ND, Fernandez-Zapico ME, Kay NE, Billadeau DD. Inhibition of glycogen synthase kinase-3 activity leads to epigenetic silencing of nuclear factor kappaB target genes and induction of apoptosis in chronic lymphocytic leukemia B cells. *Blood* 2007;**110**:735−42.
132. Hill EV, Ng TH, Burton BR, Oakley CM, Malik K, Wraith DC. Glycogen synthase kinase-3 controls IL-10 expression in $CD4^+$ effector T-cell subsets through epigenetic modification of the IL-10 promoter. *Eur J Immunol* 2015;**45**:1103−15.
133. Baindur-Hudson S, Edkins AL, Blatch GL. Hsp70/Hsp90 organising protein (hop): beyond interactions with chaperones and prion proteins. *Subcell Biochem* 2015;**78**:69−90.
134. Schmid AB, Lagleder S, Gräwert MA, Röhl A, Hagn F, Wandinger SK, et al. The architecture of functional modules in the Hsp90 co-chaperone Sti1/Hop. *EMBO J* 2012;**31**:1506−17.
135. Tsai CL, Chao AS, Jung SM, Lin CY, Chao A, Wang TH. Stress-induced phosphoprotein 1 acts as a scaffold protein for glycogen synthase kinase-3 beta-mediated phosphorylation of lysine-specific demethylase 1. *Oncogenesis* 2018;**7**:31.
136. Peng B, Wang J, Hu Y, Zhao H, Hou W, Zhao H, et al. Modulation of LSD1 phosphorylation by CK2/WIP1 regulates RNF168-dependent 53BP1 recruitment in response to DNA damage. *Nucleic Acids Res* 2015;**43**:5936−47.
137. Ramms B, Pollow DP, Zhu H, Nora C, Harrington AR, Omar I, et al. Systemic LSD1 inhibition prevents aberrant remodeling of metabolism in obesity. *Diabetes* 2022;**71**:2513−29.
138. McNamara KM, Harwood DT, Simanainen U, Walters KA, Jimenez M, Handelsman DJ. Measurement of sex steroids in murine blood and reproductive tissues by liquid chromatography-tandem mass spectrometry. *J Steroid Biochem Mol Biol* 2010;**121**:611−8.
139. Dorgan JF, Stanczyk FZ, Kahle LL, Brinton LA. Prospective case-control study of premenopausal serum estradiol and testosterone levels and breast cancer risk. *Breast Cancer Res* 2010;**12**:R98.
140. Fourkala EO, Zaikin A, Burnell M, Gentry-Maharaj A, Ford J, Gunu R, et al. Association of serum sex steroid receptor bioactivity and sex steroid hormones with breast cancer risk in postmenopausal women. *Endocr Relat Cancer* 2012;**19**:137−47.
141. Feng J, Li L, Zhang N, Liu J, Zhang L, Gao H, et al. Androgen and AR contribute to breast cancer development and metastasis: an insight of mechanisms. *Oncogene* 2017;**36**:2775−90.
142. González-Núñez D, Claria J, Rivera F, Poch E. Increased levels of 12(*S*)-HETE in patients with essential hypertension. *Hypertension* 2001;**37**:334−8.
143. Cui Y, Liu N, Ma F, Sun W, Wu H, Xu Z, et al. Role of histone modification in 12-lipoxygenase-associated p21 gene regulation. *Mol Med Rep* 2016;**14**:3978−84.
144. Calabrese CM, Valentini A, Calabrese G. Gut microbiota and type 1 diabetes mellitus: the effect of mediterranean diet. *Front Nutr* 2020;**7**:612773.
145. Wang D, Liu CD, Li HF, Tian ML, Pan JQ, Shu G, et al. LSD1 mediates microbial metabolite butyrate-induced thermogenesis in brown and white adipose tissue. *Metabolism* 2020;**102**:154011.
146. Shi Y, Lan F, Matson C, Mulligan P, Whetstine JR, Cole PA, et al. Histone demethylation mediated by the nuclear amine oxidase homolog LSD1. *Cell* 2004;**119**:941−53.
147. Ma T, Li A, Guo Y, Li S, Li M, Feng S, et al. KDM1A/LSD1 as a promising target in various diseases treatment by regulating autophagy network. *Biomed Pharmacother* 2022;**148**:112762.
148. Emond WB, Geitmann M, Jarvius M, Koehler K, Källblad P, Niklasson M, et al. Abstract 3843: LSD1 modulation by allosteric ligands. *Cancer Res* 2019;**79**:3843.
149. Emond WB, Sawant R, Geitmann M, Winquist J, Brandt P, Bremberg U, et al. Abstract 705: potentiation of immunotherapy by LSD1 modulation. *Cancer Res* 2023;**83**:705.
150. Pinkerneil M, Hoffmann MJ, Kohlhof H, Schulz WA, Niegisch G. Evaluation of the therapeutic potential of the novel isotype specific HDAC inhibitor 4SC-202 in urothelial carcinoma cell lines. *Targeted Oncol* 2016;**11**:783−98.
151. Wobser M, Weber A, Glunz A, Tauch S, Seitz K, Butelmann T, et al. Elucidating the mechanism of action of domatinostat (4SC-202) in cutaneous T cell lymphoma cells. *J Hematol Oncol* 2019;**12**:30.