Lysine-Specific Demethylase 1 in Cancers

Subjects: Cell Biology

Contributor: Aadil Javed, Teresa Rubio-Tomás, Gianluca Malagraba Papadopoulos, CARLES BARCELÓ

Epigenetic mechanisms are known to play a key role in cancer progression. Specifically, histone methylation involves reversible post-translational modification of histones that govern chromatin structure remodelling, genomic imprinting, gene expression, DNA damage repair, and meiotic crossover recombination, among other chromatin-based activities. Demethylases are enzymes that catalyse the demethylation of their substrate using a flavin adenine dinucleotide-dependent amine oxidation process. Lysine-specific demethylase 1 (LSD1) and its homolog, lysine-specific demethylase 2 (LSD2), are overexpressed in a variety of human cancer types and, thus, regulate tumour progression.

Keywords: lysine-specific demethylase 1 ; Gastric Cancer ; Liver Cancer ; Colorectal Cancer

1. Introduction

According to the World Health Organization (WHO), cancer is a group of diseases that can develop in almost any organ or tissue when a group of abnormal cells grows uncontrollably beyond its normal limits, and can then invade other tissues (metastasis). In 2020, there were more than 19 million new cancer cases and almost 10 million deaths due to cancer, making this disease the second cause of death worldwide. Furthermore, up to 30% of these deaths are due to gastrointestinal cancers [1][2].

Understanding the mechanisms of cancer is key to developing efficient and specific treatments. Acquisition of cancer hallmarks largely depends on alterations in the genomes of neoplastic cells, including genome mutations, as well as epigenetic mechanisms which affect gene expression [3][4].

Epigenetics is commonly defined as the heritable changes in gene expression or chromosomal stability by DNA methylation, histone covalent modification (methylation, acetylation, ubiquitination…), or non-coding RNAs without a change in DNA sequence. Epigenetics plays a central role in cancer by altering proto-oncogenes and tumour suppressor transcription [5]. For a long time, methylation marks in histones were thought to be irreversible until the discovery of histone demethylases [6]. There are two families of histone demethylases: the larger Jumonji domain family and the smaller flavin-dependent lysine-specific demethylase (LSD) family formed by lysine-specific demethylase 1 (LSD1) and lysine-specific demethylase 2 (LSD2) [7].

LSD1 (also referred to as KDM1A/BHC110/AOF2) was the first human histone demethylase identified (2004). The LSD1 homolog, LSD2 (also referred to as KDM1B/AOF1), was identified the same year through a domain homology search of genomic databases and became the second human histone demethylase identified [6][7][8]. Both enzymes are characterized by the presence of an amine oxidase-like domain and a Swi3p, Rsc8p, and Moira (SWIRM) domain, which are unique to chromatin-associated proteins. Other than these two domains, LSD1 and LSD2 exhibit different structural architectures facilitating their association with different protein complexes and different genomic loci [7].

There are three structural domains present in LSD1 that are well conserved including the c-terminal amino oxidase-like (AOL) domain, the SWI3/RSC8/MOIRA (SWIRM) domain, and the flexible n-terminal region. The catalytic region of LSD1 resides on the AOL domain, which contains two lobes where one lobe connects with SWIRM, which further contains the follistatin domain (FSD)-binding site carrying oxidation, and the second lobe functions as a substrate recognition site. Therefore, the lobes form the catalytic centre displaying demethylation activity in the cavity. AOL domain also protrudes a Tower domain accompanying alpha-helices, which forms an interaction site with repressor element 1 (RE1) silencing transcription factor (REST) corepressor (CoREST) complex and is critical for H3K4 demethylase activity of LSD1. The extra-nucleosomal DNA can bind with the AOL domain along with the CoREST complex. The nuclear localization of LSD1 depends on the flexible n-terminal region of LSD1, which is not responsible for its demethylase activity. LSD1 has a specialized SWIRM domain incapable of binding to DNA and acts as an interaction site of LSD1 with its interacting partners [6][7][8].

2. LSD1 in Gastric Cancer

LSD1 has been shown to promote gastric cancer proliferation [9]. More importantly, overexpression of LSD1 is involved in many pathological processes of gastric cancer, such as proliferation, apoptosis, and metastasis of various GC cells [10].

Recently, a number of studies have highlighted the critical roles played by long noncoding RNAs (lncRNAs) in the pathogenesis of several types of human cancer, especially in GC [11]. More importantly, lncRNAs can directly bind to LSD1 and may function as a scaffold, thereby repressing underlying Krüppel-like factor 2 (KLF2) target and large tumor suppressor kinase 2 (LATS2) expression [12]. LSD1 and lncRNAs have a role in carcinogenesis and cancer spread by suppressing tumour suppressors or activating oncogenes through various methods such as epigenetic alteration, alternative splicing, RNA decay, and posttranslational modification regulation [13]. Lysine (K)-specific demethylase 1A (LSD1) as the core of the LSD1/CoREST/REST repressor complex and histone demethylase could specifically demethylate H3K4me1/2. Recent studies have shown that multiple tumour-related lncRNAs regulated cancer progression through interactions with enhancer of Zeste 2 Polycomb repressive complex 2 subunit (EZH2) and LSD1 [9].

2.1. LSD1 and LincRNAFEZF1-AS1

LSD1 can hyperactivate GC cells aided by LincRNAFEZF1-AS1 to repress p21 expression [14]. Shin et al. showed that endogenous FEZF1-AS1 was enriched in the anti-LSD1 RIP fraction in AGS and SGC-7901 gastric adenocarcinoma cell lines, concluding that LSD1 could promote GC cell proliferation [15]. Knocking down LSD1 by si-RNA in AGS and SGC-7901 cells upregulated p21 protein levels [16]. Moreover, p21 was enhanced in AGS and SGC-7901 cells treated with an LSD1 inhibitor compared to untreated cells, suggesting that FEZF1-AS1 regulates p21 through LSD1-mediated demethylation.

2.2. LSD1 and lncRNA HOXA11-AS

HOXA11-AS is a GC–specific upregulated lncRNA since its expression levels are increased in GC compared to normal gastric tissues [17]. Sun et al. investigated the potential mechanisms of HOXA11-AS and LSD1 in GC cells, concluding that HOXA11-AS RNAs are more prevalent in the nucleus of a panel of GC cells [18]. Additionally, it was predicted that lncRNA HOXA11-AS mediates EZH2 and LSD1 interaction [19]. At the same time, DNMT1, EZH2, and LSD1 are also likely to be recruited by other sequence-specific transcription factors [20]. Since HOXA11-AS potentially binds LSD1 in GC cells, it is predicted to function as a scaffold to regulate PRSS8 and KLF2 transcription [21].

2.3. LSD1 and Long Noncoding RNA FOXD2-AS1

There are increasing data indicating that FOXD2-AS1 serves as an important modulator in biological processes and is dysregulated in GC, in which it could potentially serve as a tumour biomarker [22]. It has been shown to act as a tumour inducer in GC, in part through EphB3 inhibition through direct interaction with EZH2 and LSD1 [23]. FOXD2-AS1 accumulates in GC and is upregulated in GC cells and positively correlates with large tumour size, advanced pathological stage, and poor prognosis [23][24]. Gene set enrichment analysis in Gene Expression Omnibus (GEO) datasets revealed that cell cycle and DNA replication-associated genes were enriched in patients with high FOXD2-AS1 expression [25]. Loss of FOXD2-AS1 function inhibited cell growth through cell cycle inhibition in GC, while upregulation of FOXD2-AS1 expression promoted cancer progression [26][27].

2.4. LSD1 and LINC00673

Long noncoding RNA LINC00673 is overexpressed in GC [28], in which it acts as a scaffold for LSD1 and EZH2 and represses KLF2 and LATS2 expression. Indeed, LINC00673 binds directly to EZH2, LSD1, DNMT1, and STAU1 in GC cells. When BGC823 and AGS cells were treated with both EZH2 and LSD1 siRNAs the expression of the tumour suppressor LATS2 and KLF2 was enhanced, whereas no effect was observed on CADM4 expression [12].

3. LSD1 in Liver Cancer

The poor prognosis of HCC has been linked to the differentiation and self-renewal capacities of the cancer stem cells (CSCs), which are characterised by different cellular markers [29]. The self-renewal capacity of CSCs is a topic of interest in oncology and the mechanisms remain to be investigated; however, the tumorigenicity of these specialised cells has been associated with players involved in epigenetic dysregulation such as lysine demethylases including LSD1 that is a chromatin modification factor and acts to demethylase histone H3 lysine 9 (H3K9) along with the histone 3 lysine 4 (H3K4). These histones generally function in the regulation of stem cells and genome instability leading to cancers [30][31].

The hematopoietic and embryonic stem cells have pluripotency that is regulated from the epigenetic regulator LSD1 [32][33][34].

Since LSD1 is involved in the regulation of pluripotent cancer cells, the inhibition of this important class of enzymes poses an important treatment or targeting strategy for cancer therapy [35][36]. The development and stemness of HCC are promoted due to suppression of the negative regulators such as beta-catenin in Lgr5p cancer cells expressing higher levels of LSD1 [37]. The CSCs associated with HCC exhibit higher levels of LSD1 as compared to non-CSCs, and the higher expression of LSD1 is reduced in differentiated CSCs. The self-renewal capacity of non-CSCs is increased due to overexpression of LSD1 showing that LSD1 is involved in the tumorigenicity of HCC. The high activity of LSD1 is inversely correlated with acetylation as the level of acetylation of LSD1 is reduced in CSC, which shows higher self-renewal capability [37]. The activation of LSD1 results from the induction of sirtuin SIRT1 by Notch signalling, which is involved in the self-renewal of CSCs and represents one of the mechanisms by which LSD1 exerts its function in the promotion of HCC. CSC self-renewal mediated through Notch-3 signalling results from cancer-associated fibroblasts as upstream drivers with higher LSD1 expression. Therefore, the microenvironment of the tissue inside liver cancer plays a significant role in driving the role of LSD1 in Notch signalling and stemness of the CSCs, which can be targeted for therapeutic purposes [37].

The expression of LSD1 is higher in liver cancer tissues compared to noncancerous tissue adjacent to the tumour as determined by immunohistochemistry and Western blotting [38]. Furthermore, lower tumour stages also exhibit lower expression of LSD1 as compared to higher tumour stages. In liver cancer cell lines, the knockdown of LSD1 results in decreased proliferation along with reduced expression of cMyc and Bcl-2, implying that LSD1 is involved in the survival of cells [38]. Additionally, Kim et al. [39] estimated approximately 77% of the 303 patients with HCC (n = 303 cases of HCC) where positive for LSD1 protein expression by immunohistochemical analysis. Higher expression of LSD1 was associated with poorer outcomes for HCC, especially for disease-free survival and overall survival. The researchers also used CRISPR/Cas9 system to knock out LSD1 in HCC cell lines and showed that LSD1 is involved in the control of growth rate. Furthermore, the LSD1 knockout resulted in increased H3K9me1/2 and HeK4me1/2 levels along with reduced S-phase population, probably by targeting retinoic acid pathway [39].

LSD1 Inhibition as a Treatment Strategy for Liver Cancer

Since overexpression of LSD1 has been associated with various forms of cancer and silencing LSD1 reduces the migration, invasion, and proliferation of cancer cells, inhibition of LSD1 is considered one of the clinical interventions in liver cancer [37][38][40][41]. Therefore, LSD1 inhibitors are used as potential anti-cancer drugs [42]. Drug resistance in cancer is one of the major problems that requires attention; for example, oxaliplatin is a drug used as a chemotherapeutic agent in the therapy of HCC. However, drug resistance to oxaliplatin is a challenge for healthcare professionals and currently jeopardizes its use as a therapy for HCC. One of the mechanisms by which HCC attains drug resistance is via up-regulation of long non-coding RNAs such as LINC01134. The LINC01134 promoter is demethylated by LSD1 and leads to up-regulation of LINC01134, which, in turn, stabilizes p62 and assists in the activation of anti-oxidative stress pathway in HCC tissues and cells [43]. Therefore, LSD1 inhibition by specific inhibitors can be a potential option against chemo-resistance in HCC. Recently, novel small molecule inhibitors against LSD1, such as coumarin analogues and benzofuran derivatives, have been synthesized and can be utilized for targeting the cellular activity of LSD1 [44][45]. Moreover, tertiary sulphonamide derivatives exhibiting dual properties of inhibition of tubulin polymerization and LSD1 inhibition have recently been implicated as potential treatment for liver cancer [46].

4. LSD1 in Colorectal Cancer

LSD1 has been reported to be overexpressed in CRC. Overexpression of LSD1 in CRC, as in various other cancer types, facilitates proliferation, migration, invasion and stemness, and is associated with higher TNM stages [47][48][49]. Despite these findings being coherent with other studies about LSD1 in cancer, other studies suggest that LSD1 is negatively associated with CRC tumorigenesis. Ramírez-Ramírez et al. established that loss of LSD1 is significantly associated with metastasis to lymph nodes and TNM stages III-IV after analysing CRC tissues. The data suggest that LSD1 gene suppression is key during metastasis. These opposite facts may be due to the genetic background of the cells as well as the effect of environmental signals on LSD1. Additionally, consider that metastasis is a different process from carcinogenesis itself [50]. Furthermore, Carvalho et al. established that those patients who display low LSD1 expression levels (analysed by immunohistochemistry) in their CRC tumours experienced significantly lower disease-specific survival and disease-free survival. In this case, these results may differ from other studies with limitations such as low sample size, different methods to assess LSD1 expression and unknown factors in the genetic and/or environment background which may affect LSD1 regulation [51].

As LSD1 has been associated with invasion and metastasis in some cancer types, the association between LSD1 and stemness features in CRC has been studied by analysing CD133+ CRC cells. CD133 is a surface marker for CRC stem cells associated with higher viability and colony formation rate. LSD1 expression is higher in CD133+ CRC cells and is associated with stemness, not only in vitro, but in vivo as well (xenograft assays using SW620 in BALB/c mice). LSD1 knockdown increases the apoptotic rate and further decreases cell viability, colony formation rate, migration, and invasion of CD133+ cells in response to anti-cancer drugs [47].

To better understand the role of LSD1 in CRC, Chen et al. performed an LSD1 downstream target analysis in which they found 4 key LSD1-target genes associated with proliferation, metastasis, and invasion: CABYR, FOX2, TLE4 and CDH1. Moreover, they established that LSD1 overexpression mediates CABYR and CDH1 downregulation by decreasing the levels of H3K4me1 and H3K4me2 at their promoter regions [48].

Some studies associate LSD1 with PI3K/AKT, thus partly explaining LSD1-mediated cell proliferation. LSD1 correlates with AKT phosphorylation (pS473-AKT). LSD1 regulation effects on pS473-AKT do not rely on LSD1 catalytic activity, but rather on its scaffolding function for the CoREST complex. By regulating AKT, LSD1 regulates Snail protein stability, an epidermal-mesenchymal promoting transcription factor, at least in PIK3CA mutated cells in which LSD1 is highly expressed [52]. LSD1 in CRC also affects PI3K/AKT via RIOK1. Furthermore, LSD-dependent demethylation of RIOK1 in CRC significantly stabilizes RIOK1 proteins, promoting CRC cell proliferation and migration through PI3K/AKT [53].

LSD1 not only affects the proliferation process of CRC cells, but also the differentiation process. In BRAF mutant CRC, LSD1 is required for maintenance of enteroendocrine progenitors. Thus, LSD1 is associated with a secretory phenotype in BRAF mutant CRC. Not only is LSD1 associated with the differentiation of enteroendocrine cells, but it is also associated with TFF3 expression and protein secretion, which is critical for cell survival during growth factor signalling; in fact, it is involved in AKT phosphorylation in S437 [49].

In terms of LSD1 regulation, after screening an 80-gene deubiquitinase bank, the USP38 protein was identified as a LSD1 deubiquitinase stabilizing its protein levels via posttranslational modification. Therefore, by removing the ubiquitin chain from the LSD1 protein, USP38 enhances the activity of the signalling pathways activated by LSD1, enhancing proliferation, colony formation and antiapoptotic proteins [54].

Other relevant proteins have been positively correlated with LSD1, such as Tenascin C (TNC), and Tetraspanin 8 (TSPAN8), among others [55][56]. In fact, data show that TSPAN8, a transmembrane protein, enhances the tumorigenicity of CRC as it produces the same effects as LSD1. It has been established that LSD1 upregulates TSPAN8 reducing H3K9me2 occupancy on its promoter. Considering that TSAPN8 and LSD1 depletion results in an upregulation of E-cadherin and ZO-1, and a downregulation of n-cadherin, Vimentin, Slug and Snail, TSPAN8 may promote epithelial-mesenchymal transition in an LSD-1 dependent manner [56].

Finally, in addition to the aforementioned pathways, LSD1 plays a significant role in lipid regulation in CRC. As in vitro data suggest, LSD1 may play a critical role in cancer lipid metabolism. Treatment with an LSD1 inhibitor produces lipid dysregulation specially in sphingolipids and glycolipids, enhancing lipids such as ceramides and sphingomyelins. These lipids are bioactive and are involved in signalling pathways including apoptosis. Therefore, these findings may establish a connection between LSD1-mediated apoptosis and lipid metabolism [57].

LSD1-Associated Noncoding RNAs Involved in Colorectal Cancer Progression

Several long noncoding RNAs (lncRNAs) have been associated with LSD1 in CRC. Pseudogene-expressed lncRNA DUXAP10 is upregulated in human CRC and positively correlates with tumour size, TNM stage and lymph node metastasis. Thanks to RNA-protein interaction prediction and posterior ChIP assays, it has been established that DUXAP10 binds to LSD1 in some CRC cell lines mediating H3K4me2 demethylation in the p21 and PTEN promoter regions, which explains the DUXAP10 proliferation effects [58]. Similarly, lncRNA DUXAP8 is upregulated in human CRC cells and accelerates their proliferation via binding to LSD1 and EZH2 [59]. In addition to the aforementioned lncRNAs, ZEB2-AS1 and HOXA-AS2 are upregulated in CRC and are associated with increased proliferation rate, tumour size, higher TNM stage and lymph node metastasis. Both ZEB-AS1 and HOXA-AS2 bind to LSD1 possibly accelerating the cell proliferative rate [60][61]. Regarding HOXA-AS2, data suggest that it binds to LSD1 and silences p21 and KLF2 transcription as it enhances H3K4me2 demethylation in their promoters [61].

MicroRNAs are other important noncoding RNAs in cancer. miR-137-3p is one of the microRNAs that are downregulated in various cancers, including CRC. Its downregulation is associated with invasiveness of CRC cells. This microRNA negatively regulates LSD1 expression, thereby decreasing cell adhesion and migration. miR-137-3p and LSD1 both

respond to hypoxia and data suggest that a hypoxic CRC environment could induce mi-R-137-3p repression, thus derepressing LSD1 expression to induce the EMT program and tumour metastasis [62].

References

1. Cancer. 2022. Available online: https://www.who.int/news-room/fact-sheets/detail/cancer (accessed on 15 January 2022).
2. Global Cancer Observatory. International Agency for Research on Cancer. 2022. Available online: https://gco.iarc.fr/ (accessed on 15 January 2022).
3. Hanahan, D.; Weinberg, R.A. Hallmarks of cancer: The next generation. Cell 2011, 144, 646–674.
4. Hanahan, D. Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022, 12, 31–46.
5. Nirmaladevi, R.; Ilango, S.; Paital, B.; Jayachandran, P.; Padma, P.R. Epigenetic alterations in cancer. Front. Biosci. 2020, 25, 1058–1109.
6. Burg, J.M.; Link, J.E.; Morgan, B.; Heller, F.J.; Hargrove, A.E.; McCafferty, D.G. KDM1 class flavin-dependent protein lysine demethylases. Biopolymers 2015, 104, 213–246.
7. Maiques-Diaz, A.; Somervaille, T.C. LSD1: Biologic roles and therapeutic targeting. Epigenomics 2016, 8, 1103–1116.
8. Perillo, B.; Tramontano, A.; Pezone, A.; Migliaccio, A. LSD1: More than demethylation of histone lysine residues. Exp. Mol. Med. 2020, 52, 1936–1947.
9. Liu, Y.-W.; Xia, R.; Lu, K.; Xie, M.; Yang, F.; Sun, M.; De, W.; Wang, C.; Ji, G. LincRNAFEZF1-AS1 represses p21 expression to promote gastric cancer proliferation through LSD1-Mediated H3K4me2 demethylation. Mol. Cancer 2017, 16, 39.
10. Majello, B.; Gorini, F.; Saccà, C.D.; Amente, S. Expanding the Role of the Histone Lysine-Specific Demethylase LSD1 in Cancer. Cancers 2019, 11, 324.
11. Collette, J.; Le Bourhis, X.; Adriaenssens, E. Regulation of Human Breast Cancer by the Long Non-Coding RNA H19. Int. J. Mol. Sci. 2017, 18, 2319.
12. Huang, M.; Hou, J.; Wang, Y.; Xie, M.; Wei, C.; Nie, F.; Wang, Z.; Sun, M. Long Noncoding RNA LINC00673 Is Activated by SP1 and Exerts Oncogenic Properties by Interacting with LSD1 and EZH2 in Gastric Cancer. Mol. Ther. 2017, 25, 1014–1026.
13. Takeiwa, T.; Ikeda, K.; Mitobe, Y.; Horie-Inoue, K.; Inoue, S. Long Noncoding RNAs Involved in the Endocrine Therapy Resistance of Breast Cancer. Cancers 2020, 12, 1424.
14. Ocker, M.; Al Bitar, S.; Monteiro, A.C.; Gali-Muhtasib, H.; Schneider-Stock, R. Epigenetic Regulation of p21cip1/waf1 in Human Cancer. Cancers 2019, 11, 1343.
15. Shin, T.-J.; Lee, K.-H.; Cho, J.-Y. Epigenetic Mechanisms of LncRNAs Binding to Protein in Carcinogenesis. Cancers 2020, 12, 2925.
16. Etani, T.; Naiki, T.; Naiki-Ito, A.; Suzuki, T.; Iida, K.; Nozaki, S.; Kato, H.; Nagayasu, Y.; Suzuki, S.; Kawai, N.; et al. NCL1, A Highly Selective Lysine-Specific Demethylase 1 Inhibitor, Suppresses Castration-Resistant Prostate Cancer Growth via Regulation of Apoptosis and Autophagy. J. Clin. Med. 2019, 8, 442.
17. Bure, I.; Nemtsova, M. Methylation and Noncoding RNAs in Gastric Cancer: Everything Is Connected. Int. J. Mol. Sci. 2021, 22, 5683.
18. Sun, M.; Nie, F.; Wang, Y.; Zhang, Z.; Hou, J.; He, D.; Xie, M.; Xu, L.; De, W.; Wang, Z.; et al. LncRNA HOXA11-AS Promotes Proliferation and Invasion of Gastric Cancer by Scaffolding the Chromatin Modification Factors PRC2, LSD1, and DNMT1. Cancer Res. 2016, 76, 6299–6310.
19. Abdullah, O.; Alhosin, M. HAUSP Is a Key Epigenetic Regulator of the Chromatin Effector Proteins. Genes 2022, 13, 42.
20. Morlando, M.; Fatica, A. Alteration of Epigenetic Regulation by Long Noncoding RNAs in Cancer. Int. J. Mol. Sci. 2018, 19, 570.
21. Uchida, S.; Kauppinen, S. Long Non-Coding RNAs in Liver Cancer and Nonalcoholic Steatohepatitis. Non-Coding RNA 2020, 6, 34.
22. Han, T.-S.; Hur, K.; Cho, H.-S.; Ban, H.S. Epigenetic Associations between lncRNA/circRNA and miRNA in Hepatocellular Carcinoma. Cancers 2020, 12, 2622.

23. Xu, T.-P.; Wang, W.-Y.; Ma, P.; Shuai, Y.; Zhao, K.; Wang, Y.-F.; Li, W.; Xia, R.; Chen, W.-M.; Zhang, E.-B.; et al. Upregulation of the long noncoding RNA FOXD2-AS1 promotes carcinogenesis by epigenetically silencing EphB3 through EZH2 and LSD1, and predicts poor prognosis in gastric cancer. Oncogene 2018, 37, 5020–5036.

24. Schwarzmueller, L.; Bril, O.; Vermeulen, L.; Léveillé, N. Emerging Role and Therapeutic Potential of lncRNAs in Colorectal Cancer. Cancers 2020, 12, 3843.

25. Siddaiah, R.; Oji-Mmuo, C.; Montes, D.; Fuentes, N.; Spear, D.; Donnelly, A.; Silveyra, P. MicroRNA Signatures Associated with Bronchopulmonary Dysplasia Severity in Tracheal Aspirates of Preterm Infants. Biomedicines 2021, 9, 257.

26. Barth, D.; Juracek, J.; Slaby, O.; Pichler, M.; Calin, G. lncRNA and Mechanisms of Drug Resistance in Cancers of the Genitourinary System. Cancers 2020, 12, 2148.

27. Gianì, F.; Vella, V.; Tumino, D.; Malandrino, P.; Frasca, F. The Possible Role of Cancer Stem Cells in the Resistance to Kinase Inhibitors of Advanced Thyroid Cancer. Cancers 2020, 12, 2249.

28. Su, S.-C.; Lin, C.-W.; Ju, P.-C.; Chang, L.-C.; Chuang, C.-Y.; Liu, Y.-F.; Hsieh, M.-J.; Yang, S.-F. Association of LINC00673 Genetic Variants with Progression of Oral Cancer. J. Pers. Med. 2021, 11, 468.

29. Tsuchiya, H.; Shiota, G. Clinical and Biological Implications of Cancer Stem Cells in Hepatocellular Carcinoma. Yonago Acta Med. 2021, 64, 1–11.

30. Hayami, S.; Kelly, J.D.; Cho, H.-S.; Yoshimatsu, M.; Unoki, M.; Tsunoda, T.; Field, H.I.; Neal, D.E.; Yamaue, H.; Ponder, B.A.; et al. Overexpression of LSD1 contributes to human carcinogenesis through chromatin regulation in various cancers. Int. J. Cancer 2011, 128, 574–586.

31. Wu, Y.; Wang, Y.; Yang, X.H.; Kang, T.; Zhao, Y.; Wang, C.; Evers, B.M.; Zhou, B.P. The Deubiquitinase USP28 Stabilizes LSD1 and Confers Stem-Cell-like Traits to Breast Cancer Cells. Cell Rep. 2013, 5, 224–236.

32. Adamo, A.; Barrero, M.; Belmonte, J.C.I. LSD1 and pluripotency: A new player in the network. Cell Cycle 2011, 10, 3215–3216.

33. Whyte, W.A.; Bilodeau, S.; Orlando, D.A.; Hoke, H.A.; Frampton, G.M.; Foster, C.T.; Cowley, S.M.; Young, R.A. Author Correction: Enhancer decommissioning by LSD1 during embryonic stem cell differentiation. Nature 2018, 562, E24.

34. Thambyrajah, R.; Mazan, M.; Patel, R.; Moignard, V.R.; Stefańska, M.; Marinopoulou, E.; Li, Y.; Lancrin, C.; Clapes, T.; Möröy, T.; et al. GFI1 proteins orchestrate the emergence of haematopoietic stem cells through recruitment of LSD1. Nat. Cell Biol. 2016, 18, 21–32.

35. Choi, H.-J.; Park, J.-H.; Park, M.; Won, H.-Y.; Joo, H.-S.; Lee, C.H.; Lee, J.-Y.; Kong, G. UTX inhibits EMT-induced breast CSC properties by epigenetic repression of EMT genes in cooperation with LSD1 and HDAC1. EMBO Rep. 2015, 16, 1288–1298.

36. Mohammad, H.P.; Smitheman, K.N.; Kamat, C.D.; Soong, D.; Federowicz, K.E.; Van Aller, G.S.; Schneck, J.L.; Carson, J.D.; Liu, Y.; Butticello, M.; et al. A DNA Hypomethylation Signature Predicts Antitumor Activity of LSD1 Inhibitors in SCLC. Cancer Cell 2015, 28, 57–69.

37. Lei, Z.-J.; Wang, J.; Xiao, H.-L.; Guo, Y.; Wang, T.; Li, Q.; Liu, L.; Luo, X.; Fan, L.-L.; Lin, L.; et al. Lysine-specific demethylase 1 promotes the stemness and chemoresistance of Lgr5+ liver cancer initiating cells by suppressing negative regulators of β-catenin signaling. Oncogene 2015, 34, 3188–3198.

38. Zhao, Z.-K.; Dong, P.; Gu, J.; Chen, L.; Zhuang, M.; Lu, W.-J.; Wang, D.-R.; Liu, Y.-B. Overexpression of LSD1 in hepatocellular carcinoma: A latent target for the diagnosis and therapy of hepatoma. Tumor Biol. 2013, 34, 173–180.

39. Kim, S.; Bolatkan, A.; Kaneko, S.; Ikawa, N.; Asada, K.; Komatsu, M.; Hayami, S.; Ojima, H.; Abe, N.; Yamaue, H.; et al. Deregulation of the Histone Lysine-Specific Demethylase 1 Is Involved in Human Hepatocellular Carcinoma. Biomolecules 2019, 9, 810.

40. Lee, J.-Y.; Park, J.-H.; Choi, H.-J.; Won, H.-Y.; Joo, H.-S.; Shin, D.-H.; Park, M.K.; Han, B.; Kim, K.P.; Lee, T.J.; et al. LSD1 demethylates HIF1α to inhibit hydroxylation and ubiquitin-mediated degradation in tumor angiogenesis. Oncogene 2017, 36, 5512–5521.

41. Mould, D.; McGonagle, A.E.; Wiseman, D.; Williams, E.L.; Jordan, A.M. Reversible Inhibitors of LSD1 as Therapeutic Agents in Acute Myeloid Leukemia: Clinical Significance and Progress to Date. Med. Res. Rev. 2015, 35, 586–618.

42. Fang, Y.; Liao, G.; Yu, B. LSD1/KDM1A inhibitors in clinical trials: Advances and prospects. J. Hematol. Oncol. 2019, 12, 129.

43. Ma, L.; Xu, A.; Kang, L.; Cong, R.; Fan, Z.; Zhu, X.; Huo, N.; Liu, W.; Xue, C.; Ji, Q.; et al. LSD1 -Demethylated LINC01134 Confers Oxaliplatin Resistance Through SP1 -Induced p62 Transcription in HCC. Hepatology 2021, 74, 3213–3234.

44. Sun, Y.; Lv, R.; Wu, T.; Zhang, X.; Sun, Y.; Yan, J.; Zhang, Z.; Zhao, D.; Cheng, M. Design, synthesis, and biological evaluation of coumarin analogs as novel LSD1 inhibitors. Arch. Pharm. 2021, 355, e2100311.
45. Zhang, X.; Huang, H.; Zhang, Z.; Yan, J.; Wu, T.; Yin, W.; Sun, Y.; Wang, X.; Gu, Y.; Zhao, D.; et al. Design, synthesis and biological evaluation of novel benzofuran derivatives as potent LSD1 inhibitors. Eur. J. Med. Chem. 2021, 220, 113501.
46. Ding, L.; Wei, F.; Wang, N.; Sun, Y.; Wang, Q.; Fan, X.; Qi, L.; Wang, S. Tertiary sulphonamide derivatives as dual acting small molecules that inhibit LSD1 and suppress tubulin polymerisation against liver cancer. J. Enzym. Inhib. Med. Chem. 2021, 36, 1562–1571.
47. Chen, J.; Zhao, J.; Ding, J.; Wang, Z.; Du, J.; Wu, C. Knocking down LSD1 inhibits the stemness features of colorectal cancer stem cells. Braz. J. Med. Biol. Res. 2020, 53, e9230.
48. Chen, J.; Ding, J.; Wang, Z.; Zhu, J.; Wang, X.; Du, J. Identification of downstream metastasis-associated target genes regulated by LSD1 in colon cancer cells. Oncotarget 2017, 8, 19609–19630.
49. Miller, S.A.; Policastro, R.A.; Sriramkumar, S.; Lai, T.; Huntington, T.D.; Ladaika, C.A.; Kim, D.; Hao, C.; Zentner, G.E.; O'Hagan, H.M. LSD1 and aberrant DNA methylation mediate persistence of enteroendocrine progenitors that support BRAF mutant colorectal cancer. Cancer Res. 2021, 81, 3791–3805.
50. Ramírez-Ramírez, R.; Gutiérrez-Angulo, M.; Peregrina-Sandoval, J.; Moreno-Ortiz, J.M.; Franco-Topete, R.A.; Cerda-Camacho, F.D.J.; Ayala-Madrigal, M.D.L.L. Somatic deletion of KDM1A/LSD1 gene is associated to advanced colorectal cancer stages. J. Clin. Pathol. 2020, 73, 107–111.
51. Carvalho, S.; Freitas, M.; Antunes, L.; Monteiro-Reis, S.; Vieira-Coimbra, M.; Tavares, A.; Paulino, S.; Videira, J.F.; Jerónimo, C.; Henrique, R. Prognostic value of histone marks H3K27me3 and H3K9me3 and modifying enzymes EZH2, SETDB1 and LSD-1 in colorectal cancer. J. Cancer Res. Clin. Oncol. 2018, 144, 2127–2137.
52. Miller, S.A.; Policastro, R.A.; Savant, S.S.; Sriramkumar, S.; Ding, N.; Lu, X.; Mohammad, H.P.; Cao, S.; Kalin, J.H.; Cole, P.A.; et al. Lysine-Specific Demethylase 1 Mediates AKT Activity and Promotes Epithelial-to-Mesenchymal Transition in PIK3CA-Mutant Colorectal Cancer. Mol. Cancer Res. 2020, 18, 264–277.
53. Hong, X.; Huang, H.; Qiu, X.; Ding, Z.; Feng, X.; Zhu, Y.; Zhuo, H.; Hou, J.; Zhao, J.; Cai, W.; et al. Targeting posttranslational modifications of RIOK1 inhibits the progression of colorectal and gastric cancers. eLife 2018, 7, e29511.
54. Liu, W.; Zhang, Q.; Fang, Y.; Wang, Y. The deubiquitinase USP38 affects cellular functions through interacting with LSD1. Biol. Res. 2018, 51, 53.
55. Yang, Z.; Zhang, C.; Feng, Y.; Quan, M.; Cui, Y.; Xuan, Y. Tenascin-C predicts poor outcomes for patients with colorectal cancer and drives cancer stemness via Hedgehog signaling pathway. Cancer Cell Int. 2020, 20, 122.
56. Zhang, H.-S.; Liu, H.-Y.; Zhou, Z.; Sun, H.-L.; Liu, M.-Y. TSPAN8 promotes colorectal cancer cell growth and migration in LSD1-dependent manner. Life Sci. 2020, 241, 117114.
57. Li, Y.; Qian, X.; Lin, Y.; Tao, L.; Zuo, Z.; Zhang, H.; Yang, S.; Cen, X.; Zhao, Y. Lipidomic profiling reveals lipid regulation by a novel LSD1 inhibitor treatment. Oncol. Rep. 2021, 46, 233.
58. Lian, Y.; Xu, Y.; Xiao, C.; Xia, R.; Gong, H.; Yang, P.; Chen, T.; Wu, D.; Cai, Z.; Zhang, J.; et al. The pseudogene derived from long non-coding RNA DUXAP10 promotes colorectal cancer cell growth through epigenetically silencing of p21 and PTEN. Sci. Rep. 2017, 7, 7312.
59. Gong, A.; Huang, Z.; Ge, H.; Cai, Y.; Yang, C. The carcinogenic complex lncRNA DUXAP8/EZH2/LSD1 accelerates the proliferation, migration and invasion of colorectal cancer. J. Buon. 2019, 24, 1830–1836.
60. Wu, X.; Zhu, H.; Xie, Y.; Gu, X.; Zhang, L.; Huang, L. Knockdown of ZEB2-AS1 inhibits cell invasion and induces apoptosis in colorectal cancer. J. BUON 2020, 25, 194–201.
61. Ding, J.; Xie, M.; Lian, Y.; Zhu, Y.; Peng, P.; Wang, J.; Wang, L.; Wang, K. Long noncoding RNA HOXA-AS2 represses P21 and KLF2 expression transcription by binding with EZH2, LSD1 in colorectal cancer. Oncogenesis 2017, 6, e288.
62. Ding, X.; Zhang, J.; Feng, Z.; Tang, Q.; Zhou, X. MiR-137-3p Inhibits Colorectal Cancer Cell Migration by Regulating a KDM1A-Dependent Epithelial–Mesenchymal Transition. Am. J. Dig. Dis. 2020, 66, 2272–2282.