

# Lysine-Specific Demethylase 2 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.

Gastric Cancer

Liver Cancer

Colorectal Cancer

lysine-specific demethylase 2

## 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].

LSD2 also referred to as AOF1 and KDM1B is a homolog of LSD1 possessing FAD-dependent amino-oxidase activity with no specificity towards non-histone substrates and specifically demethylates H3K4me1/2 along with H3K9me2 in the regions of the promoter genes associated with NF- $\kappa$ B proteins. The protruding TOWER domain is absent in LSD2 and it displays both AOL and SWIRM domains. Both LSD1 and LSD1 are known to exhibit FAD-demethylation activity, however, these proteins have other functions in cells including gene enhancer, promoter-binding, transcriptional repression, and activation properties. LSD2 changes the methylation dynamics of key transcriptional proteins such as NSD3, Cyclin T1, and Poly II and is known to interact with these transcriptionally activated genes via their coding regions as it assists in the regulation of the elongation process of transcription [6][7][8][9].

## 2. LSD2 in Gastric Cancer

ADPGK antisense RNA 1 (ADPGK-AS1) promotes GC development through upregulation of LSD2 by sponging miR-3196, making it a potential new prognostic biomarker and therapeutic target for GC patients, and ADPGK-AS1 is dramatically overexpressed in GC cell lines compared to normal gastric epithelial cell lines [10]. Furthermore, GC patients with high ADPGK-AS1 levels had a poorer overall survival rate than GC patients with low ADPGK-AS1 levels [11]. Inhibition of ADPGKAS1 markedly accelerated GC cell apoptosis [12] and downregulated LSD2 protein levels, and this phenotype was partially rescued by inhibition of miR3196 [13]. Similarly, upon LSD2 overexpression, cell proliferation due to inhibition of ADPGKAS1 was mostly restored and the facilitating effect of inhibition of ADPGKAS1 on apoptosis was partially abolished [13]. Increased expression of ADPGKAS1 and LSD2 may be directly related to the PI3K/AKT/mTOR signalling pathway in GC tissues [10]. In addition, ADPGKAS1 downregulates p53 through the regulation of LSD2 [14].

## 3. LSD2 in Liver Cancer

In liver cancer, the Huh7 and Hep3b HCC cell lines exhibit upregulated LSD2 according to a comprehensive study designed to identify the targets involved in epigenetic alterations of these cells [15]. In another study involving HCC cell lines for sorafenib resistance, the expression of LSD2 did not change and LSD1 was found to be a regulator of drug resistance in which LSD2 depletion resulted in no apparent change in drug sensitivity [16]. Apart from these aforementioned studies, there is a dearth of data on LSD2 in the context of liver cancer and it is a potential subject of future research which needs to be explored.

## 4. Pancreatic Cancer

LSD1 seems to be involved in the progression of pancreatic cancer as it is a target for various long non-coding RNAs involved in this process [17]. Lian et al. [18] identified that HOXA cluster antisense RNA 2 (HOXA-AS2) exerts an oncogene function via interaction with LSD1. HOXA-AS2 is upregulated in pancreatic cancer tissue, promoting pancreatic cancer cell proliferation and reducing apoptotic rates in vitro (PANC-1 and BxPC-3 cell lines), and plays an important role in pancreatic cancer cells tumorigenesis in vivo (xenograft assays using BxPC-3 cells into BALB/c mice). Using RNA-protein interaction prediction, it was found that HOXA-AS2 binds with LSD1 and EZH2. RNA immunoprecipitation assays performed using LSD1 antibodies prove that HOXA-AS2 does, in fact, bind to LSD1 in BxPC-3 cells. Moreover, a positive correlation between LSD1 mRNA levels and HOXA-AS2 expression has been observed thanks to data on pancreatic cancer gene expression (GSE15471) obtained from the Gene Expression Omnibus database (GEO). Altogether, these results suggest that LSD1 functions as an oncogene in pancreatic cancer cells as it is involved in a lncRNA-HOXA-AS2/EZH2/LSD1 complex which promotes cell proliferation [18].

HOXA-AS2 is not the only lncRNA that has been associated with LSD1 in pancreatic cancer cells. Double homeobox A pseudogene 10 (DUXAP10)-derived lncRNA also plays an important role in pancreatic cancer cells. This lncRNA is upregulated in human pancreatic cancer tissues and is associated with poor prognosis/advanced tumour-node-metastasis (TNM) stages. According to Lian et al., DUXAP10 positively correlates with cell proliferation pathways, reduces apoptotic rates, enables higher cell migration and invasion rates in vitro (PANC-1 and BxPC-3 cell lines) and also inhibits pancreatic cancer cell tumorigenesis in vivo (xenograft assays using BxPC-3 into BALB/c mice). Since lncRNAs are known to interact with RNA binding proteins, researchers performed an RNA protein interaction prediction assay, concluding that DUXAP10 interacts with LSD1 and EZH2. This interaction was verified via RNA immunoprecipitation assays performed using LSD1 antibodies in BxPC-3 cells. Furthermore, a positive correlation was found between DUXAP10 expression and LSD1 mRNA levels. The reduction in BxPC-3 cell viability when treated with si-DUXAP10 and si-LSD1 is greater than when treated only with si-LSD1. Thus, LSD1 seems to play an important role in pancreatic cancer cell proliferation as it binds to DUXAP10 [19].

Regarding LSD2, Wang et al. proposed that it may be involved in the development of pancreatic cancer. An increased LSD2 expression in pancreatic cancer cells has been established by immunohistochemistry using an antibody against LSD2 in cancer tissue samples compared with their respective matching paracancerous tissue

samples, as well as by immunoblotting using human pancreatic cancer cell lines (BxPC-3, CFPAC-1, PANC, SW1990) and a normal human pancreatic duct epithelial cell line (HDPE6-C7). This increase in LSD2 expression is accompanied by suppression of cell proliferation and increase in apoptosis. When the pancreatic cancer cell lines PANC-1 and SW1990 are treated with shLSD2 resulting in LSD2 knockdown cells, in vitro cell growth is significantly reduced and apoptosis increases. Moreover, caspase 3 and caspase 7 levels and activity are increased in PANC-1 and SW1990 knockdown cells. Thus, LSD2 expression is an important determinant of apoptosis in these cell lines [20].

## 5. LSD2 in Colorectal Cancer

Similar to LSD1, LSD2 is upregulated in human CRC cells, both in vitro and in vivo. High levels of LSD2 promote cell proliferation, DNA synthesis, colony formation rate and colony size. Data show that LSD2 induces cell cycle progression and reduces apoptosis by reducing apoptosis inhibitor Bcl-2 levels and increasing cleaved caspase 3, cleaved caspase 9 and apoptosis sensor BAX levels. Moreover, LSD2 downregulates p53 expression through H3K4me2 demethylation in the p53 promoter region, thus driving the cell cycle through p53-p21-Rb. In fact, LSD2 is associated with a decrease in p53 and p21 protein levels and an increase of Rb protein levels [14].

This entry is adapted from [10.3390/biom12030462](https://doi.org/10.3390/biom12030462)

## 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. Niwa, H.; Sato, S.; Hashimoto, T.; Matsuno, K.; Umehara, T. Crystal Structure of LSD1 in Complex with 4-benzonitrile. *Molecules* 2018, 23, 1538.
10. Huang, Z.; Yang, H. Upregulation of the long noncoding RNA ADPGK-AS1 promotes carcinogenesis and predicts poor prognosis in gastric cancer. *Biochem. Biophys. Res. Commun.* 2019, 513, 127–134.
11. Jing, R.; Liu, S.; Jiang, Y.; Zong, W.; Ju, S.; Cui, M. Determination of serum RP11-731F5.2 as a noninvasive biomarker for gastric cancer diagnosis and prognosis. *Pathol. Res. Pract.* 2020, 216, 153261.
12. Jiang, H.-Y.; Wang, Z.-J. ADPGK-AS1 promotes the progression of colorectal cancer via sponging miR-525 to upregulate FUT1. *Eur. Rev. Med. Pharmacol. Sci.* 2020, 24, 2380–2386.
13. Hu, Z.Q.; Li, H.C.; Teng, F.; Chang, Q.M.; Wu, X.B.; Feng, J.F.; Zhang, Z.P. Long noncoding RNA MAFG-AS1 facilitates the progression of hepatocellular carcinoma via targeting miR-3196/OTX1 axis. *Eur. Rev. Med. Pharmacol. Sci.* 2020, 24, 12131–12143.
14. Cai, S.; Wang, J.; Zeng, W.; Cheng, X.; Liu, L.; Li, W. Lysine-specific histone demethylase 1B (LSD2/KDM1B) represses p53 expression to promote proliferation and inhibit apoptosis in colorectal cancer through LSD2-mediated H3K4me2 demethylation. *Aging* 2020, 12, 14990–15001.
15. Bayo, J.; Fiore, E.J.; Dominguez, L.M.; Real, A.; Malvicini, M.; Rizzo, M.; Atorrasagasti, C.; García, M.G.; Argemi, J.; Martinez, E.D.; et al. A comprehensive study of epigenetic alterations in hepatocellular carcinoma identifies potential therapeutic targets. *J. Hepatol.* 2019, 71, 78–90.
16. Huang, M.; Chen, C.; Geng, J.; Han, D.; Wang, T.; Xie, T.; Wang, L.; Wang, Y.; Wang, C.; Lei, Z.; et al. Targeting KDM1A attenuates Wnt/β-catenin signaling pathway to eliminate sorafenib-resistant stem-like cells in hepatocellular carcinoma. *Cancer Lett.* 2017, 398, 12–21.
17. Majello, B.; Gorini, F.; Saccà, C.D.; Amenta, S. Expanding the Role of the Histone Lysine-Specific Demethylase LSD1 in Cancer. *Cancers* 2019, 11, 324.
18. Lian, Y.; Li, Z.; Fan, Y.; Huang, Q.; Chen, J.; Liu, W.; Xu, H. The lncRNA-HOXA-AS2/EZH2/LSD1 oncogene complex promotes cell proliferation in pancreatic cancer. *Am. J. Transl. Res.* 2017, 9, 5496–5506.
19. Lian, Y.; Xiao, C.; Yan, C.; Chen, D.; Huang, Q.; Fan, Y.; Xu, H. Knockdown of pseudogene derived from lncRNA DUXAP10 inhibits cell proliferation, migration, invasion, and promotes apoptosis in pancreatic cancer. *J. Cell Biochem.* 2018, 119, 3671–3682.
20. Wang, Y.; Sun, L.; Luo, Y.; He, S. Knockdown of KDM1B inhibits cell proliferation and induces apoptosis of pancreatic cancer cells. *Pathol. Res. Pract.* 2019, 215, 1054–1060.

Retrieved from <https://encyclopedia.pub/entry/history/show/51156>