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Lysine-Specific Demethylase 1: A Promising Target Therapy

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Abstract

Histone demethylases are a new class of emerging epigenetic modulators. The first described histone demethylase enzyme in this group is lysine-specific demethylase 1A. It removes methyl groups from histones H3K4me1/2 and H3K9me1/2. LSD1 is abnormally overexpressed in various types of solid tumors and acute leukemias, where it impedes differentiation and contributes to cancer cell proliferation, cell metastasis and invasiveness, and is associated with inferior prognosis. LSD1 inhibitors significantly attenuate tumor progression in vitro and in vivo in a range of solid tumors and acute myeloid leukemia.

Abbreviations: ESC: Embryonic Stem Cell; MAOs: Monoamine Oxidases; FAD: Flavin Adenine Dinucleotide; LSD1: Lysine-Specific Demethylase 1; TCP: Tranylcypromine; AML: Acute Myeloid Leukemia; JMJD: JUMONJI C Domain-Containing; DNMT1: DNA-Methyltransferase 1; STAT3: Signal Transducer and Activator of Transcription 3; E2F1: E2F Transcription factor 1; 2-OG: 2-Oxoglutarate; ATRA: All Trans Retinoic Acid.

Introduction

Epigenetic events serve an important function in carcinogenesis. Post-translational Histone modifications are critical for control of transcription and chromatin architecture. Histone demethylases is a new class of emerging epigenetic modulators [1] that catalyze N-demethylation of histone lysine's [2]. Demethylation differs from histone acetylation in the fact that methylation occurs on both lysine and arginine (R), and in being linked to both transcriptional activation and repression [1]. Demethylases are divided into two subgroups based on their catalytic mechanisms: the flavin adenine dinucleotide (FAD)-dependent LSD1 and LSD2 and JMJD family containing JmjC domain [2].

The flavin adenine dinucleotide (FAD)-dependent LSD1 and LSD2

Lysine-specific demethylase 1A (LSD1), is known also as KDM1A, KIAA0601, BHC110, and AOF2) [3]. It is the first described histone demethylase enzyme. LSD1 enzyme consisted of 3 major domains: an amine oxidase (AO)-like domain, which is FAD cofactor dependent, a SWIRM domain, which is unique to chromatin-associated proteins and a coiled-coil TOWER domain [4]. It is located in the cell nucleus and is a key epigenetic regulator that acts as a histone methylation eraser. It demethylates di- and mono-methyl groups from the fourth and nine positions on histone 3 protein (H3K4me2/1 and H3K9me2/1), but not H3K4me3. This results in transcriptional repression or activation, respectively [3]. LSD1 can also remove mono- and di-methylated lysine residues from few non-histone targets (such as DNMT1, p53, E2F1, HIF-1α and STAT3) which are associated with angiogenesis, cell cycle arrest, chromatin remolding and proliferation of cancer cells [3]. In addition, LSD1 functions as a H3K9 demethylase when recruited by androgen or estrogen receptor [4]. LSD2 is also important in epigenetic regulation. LSD2 is a histone H3K4me1/2 demethylase with different structural organization and functions relative to LSD1 [2].

JMJD family containing JmjC domain

The JMJD family has key roles in cell differentiation, proliferation, and stem cell self-renewal. They oxidatively remove the trimethyl group of histone lysine residues preferably in a Fe2+ and 2-oxoglutarate (2-OG) dependent manner [2].

Lysine-specific demethylase 1A (LSD1)

LSD1 and biological functions

LSD1 is highly expressed in embryonic stem cells (ESC) and is downregulated during differentiation [3]. LSD1 shows differential expression in adult tissues [5]. It regulates vital cellular processes,

ranging from embryonic development to adult tissue homeostasis [3]. LSD1 maintains self-renewal potential of embryonic stem cells and adult stem cells and regulates cellular differentiation of stem cells in various tissues, including myogenic differentiation, adipogenesis, hematopoiesis and epithelial differentiation [6]. In hematopoiesis, LSD1 negatively regulates HSCs self-renewal and help terminal erythroid, granulocytic, and megakaryocytic maturation [3]. LSD1-defeciency causes severe pancytopenia and impaired HSCs differentiation [3]. LSD1 also plays a significant role in development, thermogenesis, inflammation, neuronal and cerebral physiology, and the maintenance of stemness in stem cells [6].

LSD1 and pathological conditions

In emergency hematopoiesis as in severe viral or bacterial infections, the inflammatory cytokines TNFα and IL1β suppress LSD1 activity and induce HSCs proliferation, differentiation, and immune cells production [3]. LSD1 participates in pathological conditions including cancer and viral infection. LSD1 is involved in various stages of cancer including development, progression, metastasis, and recurrence after therapy [3]. LSD1 is not a potent oncogene [3]. It promotes tumor-cell growth [6] and facilitates cancer cells survival [6] by regulating gene expression in favor of cancer cells adaptation to a pro-cancer microenvironment [6].

LSD1 inhibitors in clinical trials

LSD1 inhibition is a potential anti-cancer therapeutic strategy [5] due to its high enzymatic activity and level of expression in various types of tumors [4] as breast cancer, prostate cancer, neuroblastoma as well as in hematological malignancies [3]. LSD1 is considered a homology protein of MAO-A/B. Six MAO inhibitors were tested for their ability to inhibit LSD1 activity; three were non-selective (a) tranylcypromine/trans-2- phenyl cyclopropylamine (TCP/2-PCPA), (b) phenelzine, and (c) nialamide and three were selective for MAOA or MAOB (a) clorgiline, (b) deprenyl, and (c) pargyline [1].

LSD1 inhibitors in clinical trials in solid tumors

Several LSD1 inhibitors have been explored in the treatment of lung cancer and other solid tumors in clinical trials or even clinical use [6]. LSD1 inhibition in cancer cells enhances immunogenicity of tumor and secretion of chemokines that attract T cells, and reverse resistance to PD-(L)1 blockade. LSD1 inhibitors upregulate proinflammatory cytokines in Treg cells. It also promotes macrophages polarization to anti-tumor M1-like macrophages and enhances the infiltration of these macrophages and CD8 + T cells into the tumor. Furthermore, LSD1 inhibition activates innate immune cells, including macrophages and natural killer cells [6]. The insufficiency of LSD1 catalytic inhibition in some cancers may be explained by LSD1 demethylase-independent activity during carcinogenesis [2].

LSD1 inhibitors in clinical development in AML

LSD1 inhibitors are a promising epigenetic approach to treat AML. They alter stem cell programs, inhibit proliferation, and restore myeloid differentiation in AML cells. They have increased efficacy in leukemia subtypes carrying AML1 and MLL rearrangements, NPM1 mutations, and erythroid and megakaryoblastic differentiation block. Their effects are enhanced markedly when combined with histone deacetylase inhibitors (HDACs) or ATRA with little toxicity. Clinical trials are currently aim at treatment of refractory AML by blocking LSD1 activity [3].

The following LDS1 inhibitors are under clinical trial in AML

ORY-1001 induces cell differentiation followed by reduction of cell growth and clonogenicity particularly in M4 and M5 FAB subtypes and AML cells carrying MLL translocations [3]. INCB059872 (Incyte) is a potent selective LDS1 inhibitor that delays cellular proliferation and induces human AML cells differentiation [3]. T3775440 is a potent selective LSD1 inhibitor against erythroid and megakaryocytic leukemic cell lines [3]. SP2509 (Salarius Pharmaceuticals) is lethal against AML expressing NMP1 mutation and MLL-rearrangements [3].

Problems associated with LSD1 inhibitors

- The need to use more than single screening method due to the high rate of false-positive or -negative results [5].
- The difficulty to develop selective LSD1 inhibitors due to the high similarity of LSD1 with LSD2 and MAOs [5].
- Low anti-cancer potency of many LSD1 inhibitors, as many tumor suppressor genes or oncogenes are often regulated by multiple enzymes [5]. Combining LSD1 inhibitors with other drugs such as HDACs, or EZH2 (enhancer of zeste homolog 2) inhibitors may be a solution. For example, combining SP2509 with Panobinostat (HDAC inhibitor) shows promising results compared to either agent alone in AML clinical trials. Combined inhibitors of LSD1 and EZH2 act synergistically by inhibiting different histone methylation-modulating proteins with apparently opposite enzyme activities [3].
- Some LSD1 inhibitors are associated with acute anemia and decreased platelets' numbers [5].
- The different role played by LSD1 in different cancers [5].

Conclusion

LSD1 acts as a key epigenetic regulator of gene expression that controls cellular homeostasis. It can be a therapeutic target in certain diseases. Gaining an accurate understanding of the mechanism of action of LSD1 is essential for overcoming several diseases.

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