New Therapeutic Potential for Prostate Cancer

Assembly of methylated LSD1 and CHD1 drives AR-dependent transcription and translocation

Technology

Prostate cancer represents the most frequent malignant disease in men worldwide and the second leading cause of death from malignant tumors.

Dimethylation of lysine-specific demethylase 1 (LSD1) at lysine 114 (K114me2) by the histone methyltransferase G9A is a key event controlling androgen-dependent target gene transcription and TMPRSS2-ERG fusion.

Chromodomain-helicase-DNA-binding protein 1 (CHD1) is a LSD1 K114me2 reader.

Specifically preventing interaction of CHD1 with methylated LSD1 (or LSD1 methylation) severely impairs chromatin recruitment of CHD1 and androgen receptor (AR), androgen-dependent target gene transcription, chromatin loop formation at the *TMPRSS2* locus, and TMPRSS2-ERG gene fusion.

Innovation

- Specific modulation of LSD1 K114me2/ CHD1 interaction
- Supported by crystal structure of LSD1 K114me2/ CHD1 complex
- Less side effects likely - as compared to e.g. G9A inhibition
- Potential for better treatment of prostate and other tumors

Application

In tissues where AR has a pivotal physiological role i.e.:

- Treatment of prostate tumors
- Applications in breast and other cancers likely
- Control of fertility
- Treatment of Alzheimer´s & Parkinson´s disease

Developmental Status

- G9A methylates LSD1 at K114 to allow interaction with CHD1
- LSD1K114me2 / CHD1 interaction regulates recruitment of AR to chromatin, androgen-dependent target gene transcription, chromatin loop formation at the *TMPRSS2* locus, and TMPRSS2-ERG gene fusion
- LSD1 K114me2 / CHD1 interaction is a potential target to specifically block prostate tumor growth

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Therapy of Prostate Cancer

Patent Status

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Grant anticipated for any method identifying any compound inhibiting the interaction between LSD1me2 and CHD1

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Assembly of methylated LSD1 and CHD1 drives AR-dependent

Technology (continued)

Prostate cancer evolution is driven by a combination of epigenetic and genetic alterations such as coordinated chromosomal rearrangements named chromoplexy. The TMPRRS2-ERG gene fusion, found in more than 50% of all prostate tumors, is a hallmark of chromoplexy. Rearrangements such as TMPRSS2-ERG fusion have been linked to androgen signalling and depend on androgen receptor (AR)-coupled gene transcription.

We show that dimethylation of lysine-specific demethylase 1 (LSD1) at lysine 114 (K114me2) by the histone methyltransferase G9A is a key event controlling androgen dependent target gene transcription and TMPRSS2-ERG fusion and identified chromodomain-helicase-DNA-binding protein 1 (CHD1) as a LSD1 K114me2 reader and characterized the LSD1 K114me2/CHD1 recognition mode by solving the co-crystal structure.

Genome-wide analyses revealed chromatin co-localization of LSD1 K114me2, CHD1, and AR in human prostate tumor cells. Androgen treatment increased LSD1 K114me2 and CHD1 levels at AR binding regions. Importantly, preventing LSD1 methylation or interaction of CHD1 with methylated LSD1 severely impaired chromatin recruitment of CHD1 and AR, androgen-dependent target gene transcription, chromatin loop formation at the *TMPRSS2* locus, and TMPRSS2-ERG gene fusion.

Key features

- Methylation of LSD1 at K114 is executed by G9A in an androgen-dependent manner and serves as a regulatory switch to allow for interactions with CHD1. The androgen-regulated G9A/LSD1 K114me2/CHD1 circuit controls chromatin binding of AR
- Assembly of methylated LSD1 and CHD1 with AR-dependent links transcription and genomic translocations
- During AR dependent gene expression, methylation of LSD1 at K114 (by G9A and recruitment of CHD1 to AR binding regions) is a key event controlling chromatin binding of AR
- This novel mechanism is not only crucial for regulating androgen-dependent gene expression but also controls androgen-dependent chromosomal rearrangement such as the TMPRSS2-ERG oncogenic fusion and thereby provides mechanistic insight into this aspect during prostate tumor evolution
- Superimposition of the crystal structures of CHD1/LSD1 K114me2 and CHD1/H3K4me3 demonstrates a significant difference in the binding modalities, suggesting the potential to selectively target the CHD1/LSD1 K114me2 interface without affecting binding of CHD1 to H3K4me3
- Thus, it is conceivable that molecules targeting the LSD1 K114me2/CHD1 interaction selectively might represent novel first-in-class inhibitors of AR functions for the treatment of prostate cancer

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