New Therapy in Prostate Cancer
LSD1 controls Prostate Tumour Growth

Technology
The Lysine specific Demethylase 1 (LSD1) co-localises with AR in normal human prostate and in prostate tumor. LSD1 interacts with AR and stimulates AR-dependent transcription. We identify pargyline as an inhibitor of LSD1 that blocks AR-dependent transcription. Furthermore LSD1 knockdown by RNAi abrogates androgen induced transcriptional activation and cell proliferation.

Innovation
- better treatment of prostate tumor

Application
Modulation of LSD1 activity is tissues where AR has a pivotal physiological role i.e.:
- Treatment of prostate tumor
- Control of fertility
- Treatment of Alzheimer’s disease
- Treatment of Parkinson’s disease

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

Proof of Concept
Please contact us for further information.

Patent Status
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Assembly and signal-mediated regulation of the androgen-receptor/LSD1 histone demethylation complex

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Abstract

Gene regulation in eukaryotes requires the co-ordinate interplay of chromatin-modulating proteins with specific transcription factors such as the androgen receptor (AR). LSD1 (Lysine-specific demethylase 1) is a histone demethylase that removes repressive histone marks by demethylation of histone H3 at lysine 9 (H3-K9), thereby leading to de-repression of AR target genes. Importantly, we identify pargyline as an inhibitor of LSD1. Pargyline blocks demethylation of H3-K9 by LSD1 and consequently, AR-dependent transcription. Thus, modulation of LSD1 activity offers a novel strategy to regulate AR functions. Here, we link for the first time demethylation of a repressive histone mark with AR-dependent gene activation, thus providing a mechanism by which demethylase control specific gene expression.

Figure 1 LSD1 interacts with AR in vitro and in vivo. a, GST pull-down assays were performed with labeled LSD1 mutants and the corresponding bacterially expressed GST-AR fusion proteins. b, GST-AR and GST (RGBD) and GST ERG-NTD proteins were bound to glutathione-Sepharose beads. ChIP analyses demonstrate that AR and LSD1 form chromatin-associated complexes in a ligand-dependent manner. LSD1 relieves repressive histone marks by demethylation of histone H3 at lysine 9 (H3-K9), thereby leading to de-repression of AR target genes. Importantly, we identify pargyline as an inhibitor of LSD1. Pargyline blocks demethylation of H3-K9 by LSD1 and consequently, AR-dependent transcription. Thus, modulation of LSD1 activity offers a novel strategy to regulate AR functions. Here, we link for the first time demethylation of a repressive histone mark with AR-dependent gene activation, thus providing a mechanism by which demethylase control specific gene expression.

Figure 2 LSD1 expression analyses. a, Expression of LSD1 mRNA in human tissues was examined by Northern blot analyses on a Human Multiple Tissue Expression Array. b, Tissue expression array. c, TAP-LSD1/AR, or TAP-LSD1 complexes with or without pargyline. Western blots were decorated with the indicated antibodies (left panel). The presence of LSD1 antibodies (right panel).

Figure 3 LSD1 interacts with chromatin. LNCaP cells were incubated with or without R1881 (a, b, c), treated with or without pargyline (b), or transfected with siRNA; c, GST or Re-ChIP was performed with the indicated antibodies. The precipitated chromatin was amplified by PCR using primers flanking the promoter.

Conclusion:

1) LSD1 is an AR cofactor
2) LSD1 demethylates repressive histone marks H3K9 at AR regulated promoters
3) LSD1 controls androgen-dependent proliferation of prostate tumour cells
4) LSD1 is a potential target to block prostate tumour growth