5TH INTERNATIONAL CONFERENCE ON ADVANCED PHARMACOLOGY & TOXICOLOGY RESEARCH

November 14-15, 2025 | Lisbon, Portugal

Gökçe Yıldırım-Buharalıoğlu[1], Recep İlhan[2], Yaren Çakmak[1], C. Kemal Buharalıoğlu[3] and Mark Bond[4]

[1]Faculty of Pharmacy, Department of Pharmacology, Ege University, Izmir, TURKEY

[2]Faculty of Pharmacy, Department of Biochemistry, Ege University, Izmir,TURKEY

[3] Faculty of Pharmacy, Department of Pharmacology, IzmirKatip Çelebi University, Izmir,
TURKEY

[4] Translational Health Sciences (THS),Bristol Medical School (BMS), University of Bristol, Bristol, UK

KDM6A/B Mediated Epigenetic Regulation of Constitutive Androgen Receptor Expression in Prostate Cancer

Elevated androgen receptor (AR) expression is a hallmark of resistance to androgen deprivation therapy, underscoring the need to elucidate mechanisms regulating basal AR expression independently of androgen signaling. Histone H3 lysine 27 tri-methylation (H3K27me3) demethylases KDM6A and KDM6B were found to be higher in lymph node–metastatic LNCaP but not in bone or brain–metastatic PC3 and DU145cells compared with benign BPH-1cells (1). AR is constitutively expressed only in LNCaP, raising the question of whether KDM6A/B maintain this expression. To model advanced disease, castration-resistant LNCaP 104-R2 cells were also analyzed, showing 29- and 2.5-fold increases in KDM6A and KDM6B mRNA, respectively, confirmed at the protein level. AR steady-state mRNA, pre-spliced mRNA, and protein levels decreased by 80%, 81%, and 74% in LNCaP, and by 64%, 59%, and 90% in 104- R2 upon KDM6 family selective inhibitor, GSK-J4. AR target genes KLK3, NKX3.1, and TMPRSS2 were similarly reduced. KDM6A or KDM6B knockdown decreased AR mRNA in LNCaP and LNCaP 104-R2, respectively, while GSK-J4 increased H3K27me3 enrichment at the AR promoter in both cell lines, as shown by Chromatin Immunoprecipitation (ChIP). To understand the role of KDM6A/B controlling AR expression in previously reported GSK-J4- induced reduction in proliferation (1), change in phospho Retinoblastoma (pRb), phospho Akt (pAkt) and pan Akt proteinlevels were measuredby Western Blot.GSK-J4 decreased pAkt,pan- Akt, and pRb levels by 43%, 22%, and 74% in LNCaP, and nearly abolished pAkt and pRb in LNCaP 104-R2. Importantly, AR overexpression rescued siKDM6A-induced AR loss in LNCaP. In summary, KDM6A/B regulate AR expression via an H3K27me3-dependent mechanism and modulate proliferation-associated signaling, revealing a novel mechanism for KDM6A/B in controlling PCa cell growth.

Keywords

androgen receptor, KDM6A, KDM6B,GSK-J4, epigenetic, prostate cancer,

Biography

Dr. Yıldırım-Buharalıoğlu graduated top of her class from Ege University Faculty of Pharmacy and completed her MSc in Pharmacology at the same institution. She received the Overseas PhD Scholarship from the Council of Higher Education of Turkey (YÖK) and completed her PhD in Molecular Pharmacology under the supervision of Prof. Andrew Newby at the University of Bristol, UK. Upon returning to Turkey, she established her independent research program focusing on cancer epigenetics. Her TÜBİTAK (The Scientific and Technological Research Council of Turkey) supported projects investigate epigenetic mechanisms associated with metastasis and the regulation of androgen receptor expression in prostate cancer.

doi.org/10.51219/URForum.2025.Gokce-Yildirim-Buharalioglu

ISBN: 978-1-917892-28-5