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Estrogen mediated epigenetic modifications: Role in breast cancer therapy

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Estrogen signaling plays a key role in breast cancer progression. ERα is the ligand-dependent transcription factor that facilitates estrogen driven gene transcription via recruitment to the target gene chromatin. ERα signaling has the potential to contribute to epigenetic changes via histone modifications at the ERα target gene promoters and deregulation of enzymes involved in the ERα-mediated epigenetic pathway could play a vital role in ERα driven neoplastic processes. Because, epigenetic changes are reversible, they offer novel therapeutic opportunities to reverse ERα driven epigenetic changes. Estrogen receptor (ER)-associated coregulator deregulation often correlates with poor outcome. Proto-oncogene PELP1 is an ER coregulator and an independent biomarker of poor prognosis for ER-positive breast cancer. PELP1 modulates epigenetic changes on ER target gene promoters *via* an interaction with lysine-specific histone demethylase (KDM1). We targeted PELP1-KDM1 axis *in vivo*, using nanoliposomal formulation of PELP1-siRNA-DOPC administered systemically and KDM1 inhibitors to determine the therapeutic potential of targeting PELP1-KDM1 axis in ER-positive breast cancer. Our results provide the first *in vivo* data that pharmacological inhibition of KDM1 decreases tumor growth in both post-menopausal and pre-clinical ER-positive xenograft-based breast tumor models. Further, combining KDM1 targeting drugs with current endocrine therapies substantially impeded growth and restored sensitivity of therapy resistant breast cancer cells. Our data suggest inhibiting ERα-PELP1-KDM1-mediated epigenetic modifications as a potential therapeutic strategy for blocking breast cancer progression and therapy resistance

Biography

Vadlamudi received his PhD from the University of Wyoming in 1994 and completed postdoctoral studies from Harvard Medical School/Dana Farber Cancer Center. He served on the faculty at UT MD Anderson Cancer Center, Houston; LSU Health Science Center, New Orleans and currently is a Professor at UT Health Sciences Center, San Antonio. His current research interests include hormonal cancer initiation, progression and therapy resistance. His research is funded by NIH/NCI, DOD/BCRP and Komen foundation. He has published 106 papers in the area of hormonal cancer signaling in peer reviewed journals

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