Pharmacological restoration of PKD1: A novel strategy for prostate cancer therapy

Sikander M[1,2], Malik S[1,2], Rodriguez A[1,2], Ganju A[3], Hafeez BB[1,2], Halaweish FT[4], Chauhan SC[1,2], Jaggi M[1,2],

[1]Department of Immunology and Microbiology, School of Medicine, University of Texas Rio Grande Valley, McAllen, TX 78504, USA
[2]South Texas Center of Excellence in Cancer Research, School of Medicine, University of Texas Rio Grande Valley, McAllen TX 78504, USA
[3]Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
[4]South Dakota State University, Brookings, SD, USA

Background: Prostate cancer has poor prognosis owing to late diagnosis and ineffective multimodal clinical treatment. Extensive efforts are ongoing to establish methods that can resolve the expression of genes implicated in disease development and treatment. Previously, we reported that Protein Kinase D1 (PKD1), a serine threonine kinase, controls a number of tumor suppressor functions including cell aggregation, cell motility, cell proliferation, and cell invasion. Thus, PKD1 is considered as an emerging therapeutic target for prostate cancer treatment.

Objective: To investigate the restoration of PKD1 by a pharmacological modulator ormeloxifene, which showed well-defined PK/PD and safety profiles in humans.

Methods: Proliferation, clonogenicity, migration, invasion, western blotting and qPCR analysis were performed to investigate the anticancer effect of ORM, docetaxel and/or their combination on PKD1 and related signaling mechanisms in prostate cancer.

Results: ORM treatment inhibited cell proliferation, invasion, migration and colony formation abilities of prostate cancer cells in a dose-dependent manner compared to vehicle treated group. ORM treatment selectively induces the expression of PKD1 both at mRNA and protein levels in C4-2 cells. Moreover, our results have also shown that ORM effectively attenuates MTA1 expression in prostate cancer cells. MTA1 physically interact and shown to have inverse relationship with PKD1. In addition, we observed that ORM treatment enhances the therapeutic efficacy of docetaxel in C4-2 cells. Our results also indicate that ORM treatment potentiate the effects of docetaxel as determined by MTS and colony formation assays.

Conclusion: These results suggest that ORM exhibit potent anticancer activity *via* restoration of PKD1 in prostate cancer.