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Regulation of Androgen Receptor Co-Regulators by Activation of the CXCL12/CXCR4 Axis: A Microarray and Proteomics Approach

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ABSTRACT

Background: Activation of the CXCL12/CXCR4 axis is known to stimulate androgen-independent activation of the androgen receptor (AR) in the LNCaP prostate cancer cell line. In the present study, the CXCL12-stimulated expression profile of androgen responsive genes (ARGs) and AR:co-regulator protein:protein interactions has been identified by microarray and proteomic analysis, respectively.

Methods: To directly identify proteins that interacted with the AR in response to CXCL12 stimulation, LNCaP cells treated with CXCL12 were subjected to a total proteomics analysis after co-immunoprecipitation (co-IP) with anti-AR antibody. AR- interacting proteins from co-IP were pre-fractionated by SDS-PAGE, in-gel trypsin digested, and analyzed by liquid chromatography coupled to MS (nanoLC-MS/MS). Acquired MS2 data was searched using MASCOT against a SWISSProt human database. Detected proteins were analyzed by spectral counting to qualitatively determine significant changes in protein expression.

Results: Gene expression profiling and proteomics analysis of CXCL12-treated LNCaP cells indicated a robust regulation of ARGs, including known AR co-regulators and/or AR-interacting proteins. All known AR co-regulators were extracted and segregated according to their molecular function. GTF2 (Transcription factor), ARID1A (Chromatin Remodeling complex component) and PRDX1 (other function) are the AR co-regulators which showed greater than two fold more interaction with AR in response to CXCL12 treatment, and HNRNPD (Splicing and RNA metabolism) is the protein which is commonly differentially regulated in both microarray and proteomic analysis in response to CXCL12 treatment. The potential role of the above AR co-regulators in promoting the CXCL12- mediated and androgen-independent AR activation and hence the prostate cancer is yet to be elucidated.

Conclusions: These data shed new light into the role of ARGs and/or AR Co-regulators in CXCL12- mediated androgen independent activation of AR and suggests new therapeutic targets for the treatment of castration-resistant prostate cancers.