Retinoic acid-induced 2 driven polymerization of C-terminal binding proteins as novel mechanism of transcriptional regulation in castration-resistant prostate cancer

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Background & objectives

Most prostate tumors start as hormone-dependent cancers and can be treated by inhibiting androgen receptor (AR) activity. In dismal cases, patients can develop metastatic castration-resistant prostate cancer (CRPC), which is resistant to androgen deprivation therapy. On the molecular level, the histone methyltransferase enhancer of zeste homolog 2 (EZH2), as the catalytic component of the polycomb 2 complex, has been shown to promote development of CRPC by reprograming androgen receptor signaling. Previously, we found that increased retinoic acid-induced 2 (RAI2) protein concentration in primary tumors predicts early biochemical relapse of prostate cancer patients and thus might be associated with the development of CRCP.

The presence of a non-canonical tandem ALDLS motif on RAI2 protein prompted the present investigation on a possible role of a dual interaction of RAI2 with C-terminal binding proteins (CtBPs) on CRPC development at the molecular level.

Methods

To characterize the molecular interaction between RAI2 and CtBPs, we employed an integrated approach combining biophysical and structural biology techniques. For confirmation studies, we applied VCaP cells as model of CRPC and validated the clinical implications of our findings by gene expression analysis of circulating tumor cells (CTCs) isolated from metastatic prostate cancer patients.

Results

We demonstrate that the presence of the tandem ALDLS motif leads to well-defined polymerization of stagged CtBP tetramer layers. In prostate cancer cells, RAI2-mediated CtBP polymers are well visible as nuclear foci. RAI2-driven CtBP-polymerization is accompanied

by the relief of its corepressor activity and modulates posttranslational histone-modifications by EZH2. RAI2-deletion in VCaP cells causes the induction of neuroendocrine features, marked by increased expression of neuroendocrine markers and a higher nucleus-cytoplasm ratio. We found that detection of RAI2 gene expression in CTCs is a characteristic of CRPC patients.

Conclusion

We discovered tandem motif-induced CtBP assembly as a novel molecular principle of transcriptional regulation. We provided here first evidence that RAI2-driven CtBP polymerization in association with EZH2 contributes to suppress the development of neuroendocrine traits. These findings holds potential for better diagnosis of CRPC and the understanding of how CRPC can trans-differentiate into more aggressive subtypes.