The Cell--Extrinsic role of CHD1 in Prostate Cancer Development and Progression

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Background: Prostate cancer (PCa) invariably becomes refractory to androgen deprivation therapy (ADT), resulting in the development of metastatic castration resistant prostate cancer (mCRPC) with high morbidity and mortality. A majority of localized and metastatic prostate cancer shows loss of PTEN; therefore, identification of specific therapeutic targets and effective combinations for PCa harboring deficiencies of PTEN holds hope for patients with advanced PCa. mCRPC shows overwhelming de novo resistance to immune checkpoint blockade, motivating the study of tumor microenvironment to overcome this resistance. Taking advantage of the vast public available prostate cancer genome database, I identified the chromatin remodeling protein CHD1 as a synthetic essential gene in PTEN-deficient PCa through regulating NF-KB pathway genes. **Method:** To investigate CHD1 function on prostate cancer progression, I generated PB-Cre, PtenL/L, Chd1L/L and PB-Cre, PtenL/L, Smad4L/L, Chd1L/L genetically engineered mouse (GEM) models, and performed histopathology analysis, transcriptomic profiling and immunophenotype profiling. **Results:** So far, delayed tumor development, decreased lymph node metastasis has been observed in Chd1 depleted prostate tissues. Importantly, a significantly prolonged overall survival has been observed in CHD1 depletion mice, compared to mice with Pten loss PCa. To further uncover the mechanism underlying the CHD1 depletion phenotype, unbiased transcriptomic profiling was performed. In addition to several well-known oncogenic signaling pathways, such as EMT and Myc pathways, I also identified down-regulated inflammatory pathways upon CHD1 inhibition, prompting me to determine whether CHD1 affects TME remodeling in Pten-deficient PCa. Mass Cytometry (CyTOF) was also performed in PtenChd1 DKO mice to identify the immunophenotype. The data suggested that CHD1 directly regulates myeloid-derived suppressor cell (MDSCs) infiltration in prostate cancer, which play key roles in immune suppression. Meanwhile, CHD1 depletion boosted tumor-infiltrating CD8+ T-cells, rather than CD4+ T-cell, NK cells or B cells. Mechanistically, I uncovered that CHD1 directly regulates cytokine IL6 gene expression and thereby recruits MDSCs into PCa tumor, which suppresses CD8+ T cell proliferation and activity. In addition, I also evaluated the anti-tumor effects of inhibition CHD1/IL6 pathway alone or in combination with immune checkpoint blockade (ICB) in Pten deficient prostate cancer mouse model. **Conclusions:** These data suggested that CHD1 plays essential roles on PTEN-deficient PCa, and CHD1 contributes to MDACs mediated immunosuppressive TME in PTEN-deficient PCa. Targeting the CHD1/IL6 axis alone or in combination with ICB provide novel therapeutic strategies for PCa patients with PTEN loss.

Conflict of Interest: None

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