

Elevated RAD21 levels promote immune evasion in prostate cancer

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Abstract:

Background

Chromosomal instability drives aneuploidy, a hallmark of cancer characterized by chromosome copy number imbalance. In prostate cancer, high levels of aneuploidy are strongly associated with lethal disease progression and poor clinical outcomes. Our recent work identified chromosome 8q (chr8q) gain, one of the most frequent genomic alterations in prostate cancer, as a key driver of tumor progression through increased dosage of the cohesin gene *RAD21* located at the chr8q24 locus. We have also demonstrated that elevated *RAD21* promotes tumor growth by alleviating oncogenic stress and DNA damage. We therefore hypothesized that increased *RAD21* expression also enables prostate cancer cells to evade immune surveillance by suppressing stress-induced inflammatory signaling.

Methods and Results

To investigate this hypothesis, we deconvolved immune cell signatures from publicly available transcriptomic datasets and found that high *RAD21* expression is consistently associated with reduced natural killer (NK) cell infiltration in both primary and metastatic prostate tumors across multiple independent patient cohorts. In NK cell co-culture assays, *RAD21*-overexpressing cells exhibited significantly reduced susceptibility to NK cell-mediated infiltration and cytotoxicity and increased survival compared with control cells in both premalignant organoid and metastatic prostate cancer cell models. Consistent with these observations, *RAD21* overexpression reduced the expression of multiple pro-inflammatory cytokines involved in NK cell activation while increasing major histocompatibility complex class I (MHC-I) expression, a well-established mechanism of NK cell immune evasion. To explore the underlying regulatory mechanisms, we performed Hi-C to profile three-dimensional genome architecture in

metastatic prostate cancer cells with varying RAD21 expression. Although modest RAD21 overexpression produced minimal changes in global topologically associating domain (TAD) organization, it significantly remodeled local chromatin looping surrounding genes encoding MHC-I components, antigen presentation machinery, and NK cell inhibitory ligands. These chromatin alterations may represent a structural mechanism linking cohesin dosage to immune regulatory gene expression.

Conclusions

Collectively, our findings suggest that increased RAD21 dosage, frequently resulting from chr8q gain, promotes immune evasion by simultaneously reducing inflammatory signaling and remodeling chromatin architecture at immune regulatory loci. Targeting RAD21-mediated immune suppression may therefore represent a novel therapeutic strategy to restore anti-tumor immune surveillance in aggressive prostate cancer.

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Conflict of Interests Statement

N/A