CHEMERIN SUPPRESSES PROSTATE TUMOR GROWTH BY MODULATING THE RECRUITMENT OF EFFECTOR NK AND CD8+ T-CELLS INTO THE TUMOR MICROENVIRONMENT

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Background While immune checkpoint inhibitors and agonism of costimulatory molecules present an attractive therapy to stimulate leukocytes in cancer, the lack of adequate recruitment of effector cells into the tumor microenvironment (TME) often results in suboptimal immune responses. Chemerin (retinoic acid receptor responder 2, RARRES2) is an endogenous chemoattractant that is widely expressed by many tissues and recruits innate leukocytes through its receptor CMKLR1 which is expressed on NK cells, some dendritic cells, and macrophages. Previous studies show that RARRES2 is downregulated in multiple tumor types including prostate cancer. Here, using a syngeneic transgenic adenocarcinoma mouse prostate (TRAMP-C1) model, we show that forced overexpression of RARRES2 by tumor cells results in significant tumor suppression and recruitment of NK and CD8+ T-cells to the TME.

Methods Male C57/BL/6 mice were subcutaneously inoculated with either RARRES2-overexpressing, vector control (VC) or mixed (50:50; VC: RARRES2) TRAMP-C1 cells. Tumor sizes were measured every 3–4 days once they reach palpable sizes and tumor-infiltrating leukocytes (TILs) were analyzed by flow cytometry. Mice also received four injections of anti-PD1 (250 ug; intraperitoneal) or control IgG, where indicated.

Results Chemerin overexpression in TRAMP-C1 cells did not alter their phenotypic behavior in vitro, but significantly suppressed tumor growth in vivo in mice. Furthermore, we observed a significantly higher influx of NK (CD3-CD19- NK1.1+) and CD8+ T-cells (CD3+CD8+) in tumor-infiltrating leukocytes (TILs) from mice with mixed tumors compared with VC tumors. Depletion of NK cells, CD4+, or CD8+ T cells showed that NK cells and CD8+ T-cells, but not CD4+ T-cells, were required for chemerin-dependent suppression of TRAMP-C1 tumor growth. We found significant increases in splenic NK and CD8 T cells, and a concomitant significant decrease in splenic G-MDSC in mice with chemerin-expressing tumors compared to controls, suggesting chemerin expression within the TME has an effect on systemic immune responses. Treatment of control tumors with anti-PD1 checkpoint inhibition did not result in significant tumor suppression, while anti-PD1 treatment of chemerin-expressing tumors significantly reduced tumor growth, doubling the complete response rate in these unresponsive tumors.

Conclusions For the first time we have demonstrated that increasing chemerin expression within the prostate TME can suppress growth by augmenting recruitment of effector NK and CD8+ T-cells and has the potential to be combined with checkpoint inhibitors in order to improve response rates in non-responsive tumors. Overall, these data suggest that a tumor-targeted chemerin therapeutic may have potential to treat human prostate cancers.

Ethics Approval All animal studies were performed in accordance with approved Washington University (St. Louis, MO) and NIH Institutional Animal Care and Use Committee guidelines under an approved protocol (No. 20-0383).

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Abstracts

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