Chemerin augments antitumor immunity in prostate cancer via enhanced antigen presentation and NK/CD8$^+$ T cell recruitment

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Background:
Immune checkpoint inhibitors and costimulatory agonists show promise in cancer therapy but are often limited by poor effector immune cell infiltration into the tumor microenvironment (TME). Chemerin (*RARRES2*), an endogenous leukocyte chemoattractant, recruits immune cells via CMKLR1, found on NK cells, CD8$^+$ T cell-subsets, dendritic cells (DCs), and macrophages. RARRES2 is frequently downregulated in cancers including prostate cancer. This study investigates the effects of chemerin on immune recruitment, activation, and tumor suppression in a syngeneic prostate cancer model.
Methods:
Male C57BL/6 mice were subcutaneously inoculated with TRAMP-C1 prostate cancer cells overexpressing RARRES2, vector control (VC), or a 1:1 mixture. Tumor growth and tumor-infiltrating leukocytes (TILs) were assessed by flow cytometry. Mice received anti-PD-1 or isotype control antibodies where indicated. Functional roles of immune subsets were examined via *in vivo* depletion.
Results:
RARRES2 overexpression did not affect TRAMP-C1 cell proliferation *in vitro* but significantly inhibited tumor growth *in vivo*. This correlated with increased NK ($CD3^-CD19^-NK1.1^+$) and CD8$^+$ T cell ($CD3^+CD8^+$) infiltration into the TME. Depletion studies confirmed that NK and CD8$^+$ T cells, but not CD4$^+$ T cells, were essential for chemerin-driven tumor suppression. RARRES2 expression also induced systemic immune changes, including elevated splenic NK and CD8$^+$ T cells and reduced granulocytic MDSCs. While anti-PD-1 monotherapy was ineffective in control tumors, it significantly enhanced regression and complete response rates in chemerin-expressing tumors, inducing an enhanced effect on the anti-PD1 therapy. Chemerin also increased frequency and activation of cross-presenting XCR1$^+$ cDC1s, marked by higher MHC-I, CD80, and CD86 expression. *Ex vivo*, chemerin-treated DCs improved antigen presentation and antigen-specific CD8$^+$ T cell activation.
Conclusion:
This study demonstrates that chemerin expression in the prostate TME suppresses tumor growth by enhancing NK and CD8$^+$ T cell recruitment and cDC1-mediated antigen presentation. Chemerin also sensitizes tumors to PD-1 blockade, supporting its potential as an immunotherapy strategy for prostate cancers resistant to checkpoint inhibition.

Funding: PCF Young Investigator Award, ACS Research Scholar Award, Siteman Investment Program Award

COI Disclosures: RP: Advisory: Amgen, AstraZeneca, Bayer, BMS, Blue Earth Diagnostics, Dendreon, Eisai, Exelixis, Genentech/Roche, Janssen/JnJ, Macrogenics, Merck, Pfizer, Sanofi-Aventis, Tolmar Therapeutics; Research Funding: BMS, Exelixis, Janssen, Genentech/Roche, Pharmacyclics; IP/Licensing: Tempus (licensing), Pixie Biosciences (ownership, lincensing). All others: no relevant COI.