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Primary Research

TLR9 expression and secretion of LIF by prostate cancer cells stimulates accumulation and activity of polymorphonuclear MDSCs

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Abstract

Proinflammatory signals promote prostate tumorigenesis and progression, but their origins and downstream effects remain unclear. We recently demonstrated that the expression of an innate immune receptor, TLR9, by prostate cancer cells is critical for their tumor - propagating potential. We investigated whether cancer cell–intrinsic TLR9 signaling alters composition of the prostate tumor microenvironment. We generated Ras/Myc (RM9) and Myc - driven (Myc - CaP) prostate cancer cells expressing the tetracycline - inducible gene *Tlr9* (*Tlr9*^{ON}) or the control *LacZ* (*LacZ*^{ON}). When engrafted into mice and treated with tetracycline, *Tlr9*^{ON}, but not *LacZ*^{ON}, tumors showed accelerated growth kinetics compared with tumors in PBS - treated mice. *Tlr9* upregulation in cancer cells triggered the selective accumulation of CD11b^{+}Ly6G^{HI}Ly6C^{LO} myeloid cells, phenotypically similar to PMN - MDSCs. The PMN - MDSCs from tetracycline - treated RM9 - *Tlr9*^{ON} tumors increased the immunosuppressive activity of the STAT3 transcription factor, thereby more potently inhibiting T cell proliferation. We identified LIF, an IL - 6 - type cytokine and STAT3 activator, as a potential mediator of crosstalk between TLR9 - expressing prostate cancer cells and PMN - MDSCs. Antibody - mediated LIF neutralization reduced the percentage of tumor - infiltrating PMN - MDSCs and inhibited tumor growth in mice. The clinical relevance of LIF is confirmed by the correlation between *TLR9* and *LIF* expression in prostate cancer specimens. Furthermore, blood samples from patients with prostate cancer showed elevated levels of LIF and high LIFR expression on circulating PMN - MDSCs. Our results suggest that TLR9^{+} prostate cancers promote immune evasion via LIF - mediated expansion and activation of PMN - MDSCs. Finally, targeting TLR9/LIF/STAT3 signaling using oligonucleotide - based inhibitors, such as CpG - STAT3dODN, can offer new opportunities for prostate cancer immunotherapy.

Supporting Information