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Infiltrating T cells promote prostate cancer metastasis via modulation of FGF11→miRNA-541→AR→MMP9 and CCL5→AR→MMP9 signaling

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Early clinical studies suggested infiltrating T cells might be associated with poor outcomes in prostate cancer (PCa) patients. The detailed mechanism(s) how these T cells were recruited to the PCa and their contribution to PCa progression, however, remained unclear. Using human clinical PCa sample survey and *in vitro* co-culture system, we found PCa has a better capacity than surrounding normal prostate to recruit CD4(+) T cells via secreting more chemokine-CXCL9. The consequences of more recruited CD4(+) T cells in PCa cells could then enhance the PCa cell invasion. Mechanism dissection revealed that infiltrating CD(+) T cells might secrete FGF11 to suppress PCa androgen receptor (AR) signaling via up-regulation of miRNA-541 expression. The suppressed AR signaling could then enhance PCa cell invasion via up-regulation of MMP9 expression. Interruption of FGF11→miRNA-541→AR→MMP9 signaling via FGF11-siRNA or miRNA-541 inhibitor led to partially reverse the enhanced PCa cell invasion. Furthermore, cytokines array found another signaling from the CCL5→AR→MMP9 pathway might also be able to enhance PCa invasion. Interesting, down-regulated PCa AR could also recruit more T cell via a positive feedback mechanism. Finally, *in vivo* mouse models with xenograftedPCa CWR22rv1 cells with CD4(+) T (HH or Molt-3) cells confirmed *in vitro* co-culture studies and concluded that infiltrating CD4(+) T cells could promote PCa metastasis via modulation of FGF11→miRNA-541→AR→MMP9 and CCL5→AR→MMP9 signaling, which may provide us a new potential therapeutic approach to better battle PCa metastasis via targeting this newly identified signaling from infiltrated CD4(+) T cells.

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