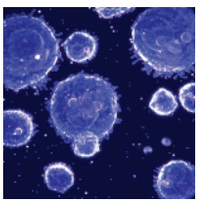
Metastasis

Major finding: IL17-producing γδ T cells drive breast cancer metastasis via neutrophil-mediated immunosuppression.

Mechanism: γδ T cells promote G-CSF–dependent expansion and polarization of neutrophils that inhibit $CD8^+$ T cells.

Impact: The γδ T cell/IL17/neutrophil axis may be a useful therapeutic target to inhibit metastatic disease.

γδ T CELLS PROMOTE BREAST CANCER METASTASIS VIA REGULATION OF NEUTROPHILS



Interaction between cancer cells and immune cells within the local tumor microenvironment and at distant sites has been shown to contribute to metastatic disease. Increased levels of neutrophils correlate with poor metastasis-specific survival in patients with breast cancer, but the contribution of neutrophils to metastasis remains unclear. Using a genetically engineered mouse model of breast cancer, Coffelt and colleagues identified a tumor-induced expansion of neutrophils and found that neutrophil depletion, specifically during the primary tumor stage, led to reduced pulmonary and lymph node metastasis without affecting primary tumor growth. Expression profiling of circulating neutrophils from tumor-bearing mice revealed upregulation of prometastatic genes as well as inducible nitric oxide synthase 2 (*Nos2*), which has previously been shown to drive immunosuppression via T-cell inhibition. Consistent with this finding, neutrophils suppressed $CD8^+$ T-cell proliferation *ex vivo*, and co-depletion of neutrophils and $CD8^+$ T cells reversed the inhibition of metastasis. Cytokine profiling of mammary tumors revealed the upregulation of factors that promote the secretion of IL17, which has been shown to drive neutrophil expansion in inflammatory disorders via systemic G-CSF induction. Elevated levels of IL17 and G-CSF were detected in the serum of tumor-bearing mice; suppression of IL17 reduced G-CSF levels, and depletion of either cytokine prevented neutrophil expansion and polarization. Importantly, total lymphocyte deficiency prevented IL17 and G-CSF upregulation, neutrophil expansion, and metastasis, suggesting that lymphocytes are the major source of IL17 in this model. Furthermore, depletion of specific T-cell subpopulations revealed that IL17-producing γδ T cells, not $CD4^+$ T cells, were required for neutrophil expansion and metastasis and were dependent on the expression of IL1β. Together, these data suggest that tumor-induced, IL17-producing γδ T cells drive metastasis via a G-CSF–mediated expansion of neutrophils with immunosuppressive function. ■

Coffelt SB, Kersten K, Doornebal CW, Weiden J, Vrijland K, Hau CS, et al. IL17-producing γδ T cells and neutrophils conspire to promote breast cancer metastasis. Nature 2015 Mar 30 [Epub ahead of print].

Prostate Cancer

Major finding: The MLL complex acts as a coactivator of AR signaling and is a potential therapeutic target in CRPC.

Mechanism: Menin is upregulated in CRPC and directly binds AR to recruit the MLL complex to AR target genes.

Impact: Small-molecule inhibitors of the menin–MLL interaction may be effective in advanced CRPC.

INHIBITION OF MLL BLUNTS AR SIGNALING AND SUPPRESSES CRPC GROWTH

The standard-of-care treatment in prostate cancer comprises surgery, radiotherapy, and androgen deprivation therapies. However, no cure is currently available for hormone-refractory castration-resistant prostate cancer (CRPC), which is a primary cause of relapse and mortality. Malik and colleagues characterized a functional interaction between the mixed-lineage leukemia (MLL) histone methyltransferase complex and androgen receptor (AR) transcriptional activity, and showed that targeting the MLL complex inhibits CRPC growth. Immunoprecipitation experiments demonstrated the interaction of AR with MLL complex proteins, including a direct interaction between the N-terminus of AR and the essential MLL cofactor menin. Depletion of MLL complex subunits resulted in a significant decrease in androgen-stimulated expression of AR target genes and diminished the growth of both prostate cancer cell lines and xenograft tumors. Genome-wide analyses showed that MLL and AR co-occupied many AR target genes and that MLL binding sites contain AR responsive elements, demonstrating the requirement of MLL as a coactivator of AR-driven transcription. In human prostate cancer samples, menin expression was elevated in metastatic CRPC compared with hormone-naïve prostate cancer and benign prostate tissue and was predictive of poor survival, supporting the idea that this MLL subunit promotes progression to CRPC. Pharmacologic inhibition of the menin–MLL interaction with the small-molecule inhibitors MI-136 or MI-503 resulted in attenuated expression of AR target genes, decreased cell viability, and increased apoptosis of prostate cancer cell lines, and suppressed the growth of castration-resistant xenograft tumors *in vivo*. Notably, treatment with these inhibitors disrupted the menin–MLL interaction, but not the menin–AR interaction, consistent with the requirement for MLL as a coactivator for AR signaling. In addition, combinatorial therapy with MI-503 and the FDA-approved anti-androgen MDV-3100 further reduced tumor growth *in vivo*. Overall, these findings highlight a functional relationship between AR and the MLL complex and provide a rationale for developing MLL-targeted therapies for the treatment of advanced CRPC. ■

Malik R, Khan AP, Asangani IA, Cieślik M, Prensner JR, Wang X, et al. Targeting the MLL complex in castration-resistant prostate cancer. Nat Med 2015;21:344–52.