The Polycomb Repressor Complex 1 Drives Double-Negative Prostate Cancer Metastasis by Coordinating Stemness and Immune Suppression

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The mechanisms that enable immune evasion at metastatic sites are poorly understood. We show that the master epigenetic regulator Polycomb Repressor Complex 1 (PRC1) drives colonization of the bones and visceral organs in double-negative prostate cancer (DNPC). In vivo genetic screening identifies CCL2 as the top pro-metastatic gene induced by PRC1. Mechanistic studies reveal that CCL2 governs self-renewal in an autocrine fashion and it induces the recruitment of M2-like tumor-associated macrophages and regulatory T cells, thus coordinating metastasis initiation with immune suppression and neoangiogenesis. We identify a catalytic inhibitor of PRC1 and show that it cooperates with immune checkpoint therapy to inhibit self-renewal and reverse immunosuppression, thus suppressing metastasis in genetically engineered mouse transplantation models of DNPC. These results reveal that PRC1 coordinates stemness with immune evasion and neoangiogenesis and point to the potential clinical utility of targeting PRC1 in DNPC.

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