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

Su W1, Han HH2, Wang Y3, Zhang B3, Zhou B4, Cheng Y1, Rumandla A3, Gurrapu S3, Chakraborty G5, Su J6, Yang G7, Liang X8, Wang G8, Rosen N1, Scher HI9, Ouerfelli O7, Giancotti FG10

(1) Molecular Pharmacology Program, Memorial Sloan Kettering Cancer Center (MSKCC), New York, NY 10065, USA.
(2) Department of Cancer Biology, The University of Texas MD Anderson Cancer Center, Unit 1906, PO Box 301429, Houston, TX 77054/77030-1429, USA; Department of Urology, Yonsei University College of Medicine, Seoul 03722, Republic of Korea.
(3) Department of Cancer Biology, The University of Texas MD Anderson Cancer Center, Unit 1906, PO Box 301429, Houston, TX 77054/77030-1429, USA.
(4) State Key Laboratory of Stem Cell and Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, China.
(5) Department of Medicine, Memorial Sloan Kettering Cancer Center (MSKCC), New York, NY 10065, USA.
(6) Cancer Biology and Genetics Program, Memorial Sloan Kettering Cancer Center (MSKCC), New York, NY 10065, USA.
(7) Organic Synthesis Core Facility, Memorial Sloan Kettering Cancer Center (MSKCC), New York, NY 10065, USA.
(8) Department of Genitourinary Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77054, USA.
(9) Genitourinary Oncology Service, Department of Medicine, MSKCC, Department of Medicine, Weill Cornell Medical College, New York, NY 10065, USA.
(10) Department of Cancer Biology, The University of Texas MD Anderson Cancer Center, Unit 1906, PO Box 301429, Houston, TX 77054/77030-1429, USA; Department of Genitourinary Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77054, USA.

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 evasision and neoangiogenesis and point to the potential clinical utility of targeting PRC1 in DNPC.

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