

CECR2 Drives Breast Cancer Metastasis by Suppressing Macrophage Inflammatory Responses

Introduction: Epigenetic and transcriptional changes are critical for metastasis, the major cause of cancer-related deaths. Metastatic tumor cells escape immune surveillance more efficiently than tumor cells in the primary sites, but the mechanisms controlling their immune evasion are poorly understood.

Methods: RNA-seq, ChIP-seq, TMA IHC staining and different mouse models were used for the study.

Results: We found that distal metastases are more immune inert with increased M2 macrophages compared to their matched primary tumors. Acetyl-lysine reader CECR2 is an epigenetic regulator upregulated in metastases and positively associated with M2 macrophages. CECR2 specifically promotes breast cancer metastasis in multiple mouse models, with more profound effect in the immunocompetent setting. Mechanistically, NF- κ B family member RELA recruits CECR2 to activate CSF1 and CXCL1, which are critical for macrophage-mediated immunosuppression at the metastatic sites. Furthermore, pharmacological inhibition of CECR2 bromodomain impedes NF- κ B-mediated immune suppression by macrophages and inhibits breast cancer metastasis.

Conclusions: These results reveal CECR2 as a key epigenetic regulator in modulating breast cancer metastatic microenvironment and a novel therapeutic target to treat metastatic breast cancer.