Metastasis

**Major finding:** Glucocorticoid receptor (GR) activity increases at distant metastatic sites in breast cancer.

**Concept:** GR activity increases expression of the kinase ROR1, which drives metastasis and reduces survival.

**Impact:** Judicious administration of corticosteroids may be required when treating cancer-related complications.

### GLUCOCORTICOID RECEPTOR ACTIVITY PROMOTES BREAST CANcer METASTASIS

Intratpatient tumor heterogeneity within and between primary tumors and their respective metastases remains a significant obstacle to the accurate diagnosis and treatment of many cancers. Obradovic and colleagues employed multiple cell line– and patient-derived xenograft models of breast cancer to explore the signaling mechanisms involved in metastasis. Following implantation and subsequent removal of primary tumor cells, metastases were found in lung, liver, spleen, and ovaries and in circulation. Transcriptional profiling revealed cancer cells clustered according to the site of metastasis, and pathway analysis indicated an increase in glucocorticoid receptor (GR) activity in metastases compared with primary tumors. Additionally, plasma levels of the stress hormones cortisol, corticosterone, and adrenocorticotropic hormone were higher in mice with metastases versus healthy control mice or mice with tumors but no metastases. Proteomic analysis from GR-activated cells revealed increased levels of kinases related to GR activation, including ROR1. In *vivo*, ROR1 levels were higher in metastases versus matched primary tumors, and a publicly available dataset of distant breast cancer metastases showed a significant positive correlation between ROR1 mRNA levels and a GR activation signature. *In vitro* activation of GR by dexamethasone increased the colonization capacity of multiple cell lines, and *in vivo* activation of GR after tumor implantation enhanced metastasis formation and reduced overall survival. Conversely, depletion of ROR1 in these models decreased colonization capacity and prolonged survival. These data indicate that increase of GR activity in breast cancer leads to upregulation of ROR1, which drives metastasis. These results also suggest that caution should be exercised when administering corticosteroids to patients receiving chemotherapy or patients with advanced disease so as to prevent treatment-induced disease progression.


Prostate Cancer

**Major finding:** Expression of delta-like protein 3 (DLL3) is a defining feature of neuroendocrine prostate cancer.

**Clinical relevance:** A DLL3-targeting antibody–drug conjugate led to a clinical and radiologic response in a patient with CRPC-NE.

**Impact:** DLL3 represents a potential therapeutic target in patients with DLL3-positive prostate cancer.

### DELTA-LIKE PROTEIN 3 IS A TARGET IN NEOuENDOCRINE PROSTATE CANCER

A subset of castration-resistant prostate cancers (CRPC) evades androgen receptor (AR)-targeted therapies by circumventing AR signaling dependencies or acquiring neuroendocrine (NE) features. Castration-resistant small cell neuroendocrine prostate cancer (CRPC-NE) is clinically aggressive and refractory to standard prostate cancer therapies, and it exhibits molecular features similar to small cell lung cancer. Preclinical studies in small cell lung cancer and neuroendocrine carcinoma utilized the antibody–drug conjugate SC16LD6.5 (rovalpituzumab tesirine), which targets the Notch pathway signaling protein delta-like protein 3 (DLL3), to achieve complete and durable eradication of tumors. Given the similarities between CRPC-NE and SCLC, Puca and colleagues assessed the expression of DLL3 and potential efficacy of SC16LD6.5 in neuroendocrine prostate cancer. Although no DLL3 expression was detected in benign and localized prostate cancers, the majority of CRPC-NE and a small percentage of CRPC adenocarcinoma expressed DLL3, and expression was associated with RB1 loss and poor overall survival. DLL3 expression correlated with the neuroendocrine markers SYP, chromogranin A, and ASCL1 as well as Notch signaling genes. In patients with CRPC-NE, DLL3 expression was lower in primary tumors than in circulating tumor cells and in tumors from multiple sites of metastasis. Treatment of DLL3-expressing CRPC-NE xenografts with SC16LD6.5 resulted in complete responses by 35 days after treatment, whereas xenografts with low DLL3 expression failed to respond to therapy. In a patient with DLL3-expressing CRPC-NE enrolled in a phase I basket trial of SC16LD6.5 for DLL3-expressing advanced solid tumors, treatment with SC16LD6.5 induced significant reductions of target nodal metastases, complete and partial responses of nontarget lesions, and no disease progression after 2 cycles of therapy. Collectively, these data highlight DLL3 as a marker for aggressive clinical features including neuroendocrine morphology and poor survival. Furthermore, they demonstrate the therapeutic potential of targeting DLL3 in patients with advanced DLL3-positive CRPC-NE, providing a possible alternative to conventional chemotherapy in the treatment of recurrent disease.

Glucocorticoid Receptor Activity Promotes Breast Cancer Metastasis


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