Metastatic Breast Cancer Cell Communication Within a Pro-Dormancy Bone Marrow Niche

Trevor T. Price1, Clara H. Lee2, Qing Cheng3, H. Kim Lyerly3,4, William E. Falg6, John L. Magnani1, Dorothy A. Sipkins1

1Division of Hematologic and Solid Tumor Malignancies, Department of Medicine, Duke University Medical Center, Durham, NC
2Department of Pathology, Duke University Medical Center, Durham, NC
3Department of Radiation Oncology, Duke University Medical Center, Durham, NC
4Department of Neurosurgery, Duke University Medical Center, Durham, NC
5Division of Hematology and Oncology, University of North Carolina at Chapel Hill, Chapel Hill, NC
6Department of Pathology, University of North Carolina at Chapel Hill, Chapel Hill, NC

Introduction

Distant metastasis is a major cause of death in breast cancer with late relapse of disease occurring after years of tumour dormancy. The bone marrow (BM) has been suggested to serve as a protective environment for disseminated breast cancer cells (BCCs), however the precise molecular signals that circulating BCCs use to identify and adhere to BM vasculature is unknown. In this study, transcriptome analysis from publically available breast cancer data sets was used to identify correlations between late recurrence of dormant breast cancer and known molecular signals associated with BM homing and retention. Analysis of tumour cells and tumour-associated stroma identified a positive correlation between CXCR4/SDF-1 and E-selectin ligand transcript expression and late recurrence. In vitro experimentation using intravital confocal microscopy revealed that E-selectin and SDF-1 possess specific roles in regulating homing, retention and proliferation of BCCs. Use of the specific E-selectin inhibitors, GM6121, significantly inhibited BCC homing to the BM. Inhibition of the SDF-1 / CXCR4 axis (using AMD-3100 or anti-CXCR4 neutralizing antibodies) had no inhibitory effect on homing, but could induce mobilization of BCCs out of the BM and into circulation. Proliferation of BCCs was also observed in BM regions in dormant BCCs were localized to sinusoidal regions where SDF-1 and E-selectin are highly expressed.

Results

Fig. 1: - Genomic Analysis of Breast Cancer Patient Data Sets

- A: EMT transcriptome analysis of breast cancer patients' data sets (TCGA, ONCO, METABRIC) reveals a significant increase in EMT markers in patients with late recurrence of breast cancer.
- B: Gene expression analysis of breast cancer patients' data sets (TCGA, ONCO, METABRIC) shows a significant increase in SDF-1 and CXCR4 expression in patients with late recurrence of breast cancer.

Discussion

This study reveals the specific roles both SDF-1 and E-selectin signaling play in trafficking of metastatic BCCs in and out of the BM. Employing available small molecule inhibitors of each pathway, GM6121 & AMD-3100, is shown to prevent homing of cells to promote mobilization of cells out of the BM, respectively, and may represent viable therapeutics for the treatment and prevention of late recurrence disease in breast cancer.