Metastasis is a multistep process that is critically dependent on the interaction of metastasizing tumor cells with cells in the local microenvironment. Within this tumor stroma, vessel-associated pericytes and myofibroblasts share a number of traits, including the upregulated expression of the transmembrane receptor endosialin (CD248). Comparative experiments in wild-type and endosialin-deficient mice revealed that stromal endosialin does not affect primary tumor growth but strongly promotes spontaneous metastasis. Mechanistically, endosialin-expressing pericytes in the primary tumor facilitate distant site metastasis by promoting tumor cell intravasation in a cell contact-dependent manner, resulting in elevated numbers of circulating tumor cells. Corresponding to these preclinical experiments, in independent cohorts of primary human breast cancers, upregulated endosialin expression significantly correlates with increased metastasis and poorer patient survival. Together, the data demonstrate a critical role for endosialin-expressing primary tumor pericytes in mediating metastatic dissemination and identify endosialin as a promising therapeutic target in breast cancer. Cancer Res; 76(18); 5313-25. ©2016 AACR.