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Introduction

More complex view of protease involvement in carcinogenesis through activation of oncogenic signaling pathways has emerged in recent years. Matriptase, the type II transmembrane serine protease was first discovered in breast cancer cell lines and is highly expressed by malignant cells in human breast carcinoma cells. This study circumvents obstacle of study that is perinatal lethality of matriptase-null mice, by employing a matriptase hypomorphic model with low levels of matriptase in the mammary gland. Previous studies have showed that HGF/c-Met signaling pathway is dysregulated in many cancer types. This signaling is regulated by activation of pro-HGF, thus identification of critical activator which can be one of the targets for therapeutic intervention of cancer. Matriptase exerts its pro-carcinogenic effect by activation of pro-HGF on the cancer cell surface leading to initiation of the c-met signaling pathway and elicitation of invasive response in breast cancer.

Targeting Matriptase in breast cancer abrogates tumor progression via impairment of stromal-epithelial growth factor signaling.

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Abstract

Matriptase is an epithelia-specific membrane-anchored serine protease that has received considerable attention in recent years because of its consistent dysregulation in human epithelial tumours, including breast cancer. Mice with reduced levels of matriptase display a significant delay in oncogene-induced mammary tumour formation and blunted tumour growth. The abated tumour growth is associated with a decrease in cancer cell proliferation. Here we demonstrate by genetic deletion and silencing that the proliferation impairment in matriptase-deficient breast cancer cells is caused by their inability to initiate activation of the c-Met signalling pathway in response to fibroblast-secreted pro-HGF. Similarly, inhibition of matriptase catalytic activity using a selective small-molecule inhibitor abrogates the activation of c-Met, Gab1 and AKT, in response to pro-HGF, which functionally leads to attenuated proliferation in breast carcinoma cells. We conclude that matriptase is critically involved in breast cancer progression and represents a potential therapeutic target in breast cancer.