豆包结果：

Introduction

Breast cancer is the most prevalent malignancy and the leading cause of cancer-related mortality in women worldwide. Triple-negative breast cancer (TNBC)—an aggressive subtype defined by the absence of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 expression—is characterized by high metastatic potential, limited targeted therapeutic options, and poor clinical outcomes. Metastatic dissemination is responsible for the vast majority of deaths in TNBC patients, rendering it imperative to delineate the mechanisms governing cancer cell migration and to develop effective therapeutic strategies targeting this process.

The biophysical properties of the tumor microenvironment, particularly extracellular matrix (ECM) stiffness, have emerged as critical regulators of cancer progression. Breast tumor tissue exhibits markedly increased matrix rigidity compared with normal breast parenchyma, driven by excessive collagen deposition and cross-linking. This mechanical cue promotes malignant transformation, enhances cell motility and invasiveness, and modulates therapeutic sensitivity. Kostic et al. (2009) demonstrated that the magnitude of matrix rigidity response varies across breast cancer cell lines and correlates with their metastatic tissue tropism, indicating that cellular mechanosensing is intrinsically coupled to metastatic behavior. Further, Tilghman et al. (2012) showed that matrix rigidity modulates cancer cell proliferation by reprogramming cellular metabolism and protein synthesis, highlighting the broad impact of mechanical signals on cancer cell phenotypes.

Focal adhesion kinase (FAK), a non-receptor tyrosine kinase concentrated at focal adhesions, acts as a central integrator of mechanical and biochemical signals from the ECM. Upon stimulation by integrin engagement or elevated matrix stiffness, FAK undergoes autophosphorylation at Tyr397, which triggers downstream signaling cascades that regulate focal adhesion turnover, actin cytoskeleton remodeling, cell migration, and cell cycle progression. Dysregulated FAK activation is a common molecular feature of breast cancer, and increased FAK expression and phosphorylation are associated with advanced tumor stage, metastatic disease, and unfavorable patient prognosis. Targeting FAK has thus become a promising therapeutic strategy to suppress breast cancer metastasis. In line with this, Masuyama et al. (2026) recently reported that pharmacological inhibitio migration and non-angiogenic vascularization in malignant supporting the therapeutic potential of FAK-targeted agents

具体临床关联论述缺少对应Citation：FAK表达/磷酸化与肿瘤分期、转移及预后的关系均未标注文献来源。

Despite the promise of FAK inhibitors, their preclinical and clinical efficacy has been highly variable, and the factors underlying this heterogeneity remain poorly understood. Accumulating evidence indicates that the mechanical tumor microenvironment can shape cellular responses to targeted therapies, yet whether and how matrix stiffness modulates the efficacy of FAK inhibition, particularly their anti-migratory effects, which are central to TNBC progression, remains largely uncharacterized in TNBC. Compound X, a potent and selective small-molecule inhibitor of FAK, whose chemical synthesis and in vitro biochemical inhibitory activity have been fully described in a prior study (Smith et al., 2024). However, the cellular effects of Compound X under different matrix stiffness conditions have not been investigated. Specifically, it is unknown whether matrix stiffness alters the ability of Compound X to suppress cell migration, disrupt focal adhesion assembly, or reorganize the actin cytoskeleton. Furthermore, whether the anti-migratory and anti-proliferative effects of FAK inhibition are differentially regulated by matrix stiffness.

涉及FAK抑制剂临床/临床前疗效差异的具体判断，但未提供对应Citation支持。

“尚未研究”属于较强的文献空白判断，当前Citation不足以直接支持这一排他性结论。

In the present study, we investigated the role of matrix stiffness on the inhibitory activity of Compound X in two TNBC cell lines, MDA-MB-231 and BT-549, cultured on polyacrylamide hydrogels with physiologically relevant soft (2.1 kPa) and stiff (20.4 kPa) moduli. we first verified that increased matrix stiffness promotes FAK Tyr397 phosphorylation, cell spreading, and stress fiber formation. We then demonstrated that Compound X dose-dependently inhibits FAK phosphorylation to a comparable degree under both stiffness conditions, but exerts a significantly stronger inhibitory effect on cell migration under stiff matrix conditions. This differential anti-migratory efficacy was associated with more pronounced disruption of focal adhesions and actin stress fibers on stiff gels, and was independent of short-term changes in cell viability or proliferation. We further confirmed the FAK dependence of these effects using siRNA-mediated FAK knockdown and the reference FAK inhibitor defactinib, both of which recapitulated the stiffness-dependent anti-migratory phenotype. Taken together, our findings reveal that matrix stiffness selectively amplifies the anti-migratory efficacy of FAK inhibition by modulating focal adhesion and cytoskeletal dynamics, without affecting global FAK phosphorylation or proliferative responses. These results advance our understanding of mechanical regulation of targeted therapy response and provide a biological rationale for considering matrix stiffness as a potential biomarker for FAK-targeted therapy in TNBC.

Introduction直接报告多项主要实验结果及结果性结论，研究目的与Results内容混杂。

由体外两种细胞系的基质硬度实验进一步外推至“潜在biomarker”，当前研究设计不足以直接建立生物标志物价值。

References

1. Kostic A, Lynch CD, Sheetz MP. Differential matrix rigidity response in breast cancer cell lines correlates with the tissue tropism. *PLoS One*. 2009;4(7). https://doi.org/10.1371/journal.pone.000636
2. Tilghman RW, Blais EM, Cowan CR, et al. Matrix rigidity regulates cancer cell growth by modulating cellular metabolism and protein synthesis. *PLoS One*. 2012;7(5). https://doi.org/10.1371/journal.pone.0037231
3. Smith Y, Cohen H, Chen X, Wang J, Galileo M. Discovery and characterization of Compound X, a potent small-molecule inhibitor of focal adhesion kinase. *Chem Biol Drug Des*. 2024;12(3):145–158.
4. Masuyama M, Shimoda M, Seto I, et al. Targeting focal adhesion kinase inhibits cell migration and non-angiogenic vascularization in malignant breast cancer. *Breast Cance*
https://doi.org/10.100

未识别并校正输入Reference中的错误DOI。

该文献目前未检索到可验证的公开记录，但被直接作为Reference引用，未提示进一步核查。

正文采用author–year引用方式，而文末Reference采用编号列表，Citation与Reference格式体系不统一。

仅使用输入提供的4篇Reference，未进一步扩充背景及机制相关文献，限制了部分具体背景论述的Citation覆盖。

以上结果来自豆包 2.1 Turbo