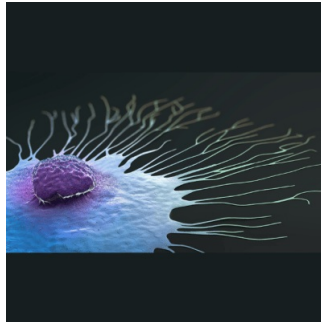


---

## Fatty Acid Metabolism Biomechanical Influence on Breast Cancer Metastasis



---

The stiffness of triple-negative breast tumours influences the aggressiveness of cancer cells and their ability to spread to other organs, according to research from the Garvan Institute of Medical Research. Soft tumour environments prime cancer cells for survival during metastasis by triggering an alternative form of metabolism. [A recent study published in Advanced Science](#) suggests that targeting altered cancer cell metabolism could enhance treatments for metastatic triple-negative breast cancer. Using biomaterials to mimic tumour properties, researchers found that cancer cells grown in soft environments were more resilient and up to 11.8 times more likely to metastasize in mouse models. Soft environments also alter cancer cells' preference for energy sources, enhancing their durability while travelling through the body. By blocking lipid metabolism, researchers reduced metastasis in cell models, highlighting a vulnerability of triple-negative breast cancers. These findings emphasise the importance of considering mechanical diversity when designing treatments for aggressive cancers and suggest the potential for targeted metabolic inhibitors to limit metastasis and improve outcomes for patients.

### Impact of ECM Dysregulation and Metabolic Flexibility in Breast Cancer Progression

The extracellular matrix (ECM) in cancer undergoes significant dysregulation, affecting both biochemical and biophysical properties, influencing cancer cell behaviour and disease progression. Changes in ECM stiffness, particularly in breast cancer, significantly impact cell behaviour within the primary tumour, affecting invasiveness, metastasis, and chemotherapy resistance. While research primarily focuses on primary tumour effects, there's a gap in understanding the long-term impact on cancer cells post-metastasis. In recent years, the role of cellular energetics in tumour progression, particularly in triple-negative breast cancer (TNBC), has gained attention. TNBC cells exhibit glycolytic dependency in the primary tumour, but their metabolic flexibility enables adaptation during metastasis. Metabolic shifts, including oxidative phosphorylation and fatty acid metabolism, promote cell survival and adaptation to secondary sites.

### Connecting Microenvironment and Metabolic Rewiring in TNBC metastasis

Experimental models show that biomechanical properties of the primary tumour microenvironment influence TNBC metastatic capacity. Softer microenvironments prime cancer cells for enhanced survival mechanisms, increasing metastatic colonisation. This priming effect is linked to metabolic re-wiring, particularly in fatty acid oxidation, which aids in secondary site colonisation. Blocking  $\beta$ 1-integrin mediated mechanosensing in stiff microenvironments recapitulates the priming effects of soft microenvironments, highlighting the importance of ECM biomechanics in metastasis.

### Implications for Breast Cancer Progression

The study discusses the biomechanical properties of solid tumours, highlighting their diversity within and between tumours. It presents findings from experiments conducted to understand how these biomechanical differences affect tumour progression, focusing on breast cancer. The study utilised various techniques to assess the stiffness of tumour tissues compared to healthy tissue. They found significant differences in stiffness, with tumours being notably stiffer. Moreover, they investigated the heterogeneity of stiffness within tumours, observing variations across different regions of a tumour. To mimic this biomechanical diversity, the researchers created hydrogels with stiffness resembling healthy and tumour tissues. They found that breast cancer cells behaved differently depending on the stiffness of the substrate they were cultured on, affecting proliferation, invasion, and metastatic potential.

### Metabolic Flexibility in Metastasis: Impact of Biomechanical Priming

The study further explored how cells primed on soft substrates exhibited enhanced metabolic activities related to fatty acid oxidation, which could influence their ability to survive and proliferate during metastasis. This metabolic shift was found to contribute to the increased spheroid-forming capacity of soft-primed cells and their enhanced ability to colonize secondary sites in vivo. By inhibiting specific integrin interactions, the researchers were able to alter cellular responses to biomechanical cues, leading to changes in metabolic profiles and metastatic behaviour.

## Clinical Implications for Tumour Microenvironment

Overall, the findings suggest that the biomechanical properties of the tumour microenvironment play a crucial role in shaping cancer cell behaviour and metastatic potential, with implications for understanding and potentially targeting metastasis in breast cancer. The primary tumour microenvironment plays a crucial role in cancer progression, influencing cell growth, metastasis, and seeding at secondary sites. Previous research has focused on the impact of increased stiffness in driving disease progression. However, there's emerging evidence indicating that softer microenvironments can also promote tumorigenicity and resistance to treatment. This study explores how changes in microenvironmental stiffness affect mammary carcinoma cells, leading to metabolic shifts and enhanced survival mechanisms. Soft microenvironments equip cancer cells with greater resistance to stress conditions, promoting lipid metabolism and fatty acid oxidation, which in turn enhances colonisation ability. Additionally, inhibiting integrin  $\beta 1$ , a protein involved in cell-matrix interactions, mimics the effects of a softer microenvironment on cellular energetics. While  $\beta 1$  integrin inhibition has shown mixed effects in previous studies, this research highlights its role in promoting metastasis.

Understanding the biomechanical heterogeneity of tumours is essential for comprehending tumour behaviour and developing effective therapeutics. This study contributes to elucidating the long-term effects of biomechanical reprogramming on cancer cell behaviour beyond the primary tumour.

Source: [Advanced Science](#)

Image Credit: [iStock](#)

Published on : Thu, 18 Apr 2024