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Atomic Force Microscopy in Cancer Research: A Nanoscale Approach to Cell Mechanics

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Introduction

Cancer progression involves a complex interplay of genetic, biochemical, and biomechanical changes in cells and their microenvironment. Atomic Force Microscopy (AFM) has emerged as a powerful tool to investigate the mechanical properties of cells at the nanoscale, offering insight into tumor development, metastasis, and therapeutic response. This article reviews the principles of AFM and its applications in cancer research, particularly in quantifying cellular stiffness, adhesion, and cytoskeletal remodeling. We highlight key findings from recent studies, examine the advantages and limitations of AFM-based techniques, and propose future directions for integrating AFM into translational cancer diagnostics and treatment monitoring. Cancer is not solely a genetic disease-it is also mechanical. Tumor cells exhibit altered mechanical properties that contribute to their ability to proliferate, invade, and metastasize. Traditional molecular and histological methods offer valuable diagnostic information, but they lack the capability to measure physical changes in cancer cells and tissues at the nanometer scale.

Description

Atomic Force Microscopy (AFM) fills this gap by providing high-resolution, label-free, and quantitative data on cell morphology and mechanics. With its ability to measure stiffness, adhesion forces, and surface topography in live cells under physiological conditions, AFM has become increasingly relevant in oncology research. AFM operates by scanning a sharp tip attached to a flexible cantilever over a sample surface. As the tip interacts with the sample, deflections of the cantilever are measured and converted into force-distance curves, from which mechanical properties can be derived. AFM force spectroscopy involves indenting the cell with a calibrated tip and analyzing the force-indentation response using contact mechanics models (e.g., Hertz, Sneddon). Cancer cells are often mechanically softer than their non-cancerous counterparts. Decreased stiffness is associated with enhanced deformability, allowing tumor cells to migrate through tight extracellular spaces. Breast, ovarian, and prostate cancer cells have consistently shown lower Young's modulus values compared to healthy epithelial cells. AFM has been used to classify cell lines based on metastatic potential, providing a mechanical phenotype of malignancy. AFM studies have revealed that changes in cell stiffness are closely linked to cytoskeletal remodeling. Actin filament reorganization, common in metastatic cells, leads to a more compliant cytoplasm and irregular surface morphology. AFM, when combined with fluorescence microscopy, allows correlation between cytoskeletal protein expression and mechanical measurements. AFM enables the quantification of cell–substrate and cell–cell adhesion forces. These measurements are crucial in understanding cancer cell detachment, migration, and invasion Cancer cells often exhibit reduced adhesion to the extracellular matrix, promoting mobility. Functionalized AFM tips (e.g., coated with ligands or antibodies) can probe specific receptor–ligand interactions involved in metastasis.

Treated cancer cells often show increased stiffness, correlating with reduced viability and proliferation. Time-lapse AFM imaging can monitor mechanical changes in real time, providing early indicators of drug efficacy before morphological alterations become visible. Differentiating benign vs. malignant tissues based on stiffness. Identifying mechanical signatures of drug-resistant phenotypes. Using primary tumor cells for personalized drug screening. Emerging portable and high-throughput AFM platforms are making these clinical applications more feasible. Single-cell measurements are time-consuming and labor-intensive. Maintaining physiological conditions and consistent cell attachment is critical. Mechanical properties vary with cell cycle, morphology, and local microenvironment. Classical contact mechanics models may not accurately describe viscoelastic or heterogeneous cells. Addressing these limitations requires advances in automation, integration with other analytical tools, and more sophisticated data analysis algorithms. Combining AFM with genomics, proteomics, and metabolomics could link mechanical changes to molecular alterations. Hybrid systems combining AFM with confocal or super-resolution microscopy will provide holistic cellular profiles. Machine learning can assist in pattern recognition and classification based on AFM datasets. Applying AFM to organoids and spheroids will better simulate in vivo tumor environments. These advancements will enhance AFM's utility as both a basic research and clinical tool in oncology [1-5].

Conclusion

Atomic Force Microscopy provides a unique window into the biomechanical landscape of cancer. By revealing changes in cell stiffness, adhesion, and structure at the nanoscale, AFM complements molecular diagnostics and deepens our understanding of tumor biology. As technologies mature, AFM is poised to play a central role in the development of novel diagnostics, targeted therapies, and precision medicine strategies in cancer care.

Acknowledgment

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Conflict of Interest

None.

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