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Hydrogel Formulations to Investigate Lung Cancer Mechanism

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INTRODUCTION: Lung cancer remains a leading cause of cancer-related deaths worldwide, largely due to late diagnosis and the complexity of the tumor microenvironment (TME).[1] A key factor in lung cancer is the extracellular matrix (ECM), a 3D network composed of structural proteins, glycoproteins, proteoglycans, and growth factors that together regulate cell adhesion, proliferation, and signaling. ECM architecture and its changes are closely related to cancer mechanisms.[2] Thus, physiological models that recapitulate ECM composition and mechanics are essential. 2D cultures fail to replicate the organization and biochemical and mechanical signals of the TME, whereas microfluidic platforms offer dynamic, 3D cell culture systems hydrogel-integrated.[3] A broad range of biomaterials (synthetic, semi-synthetic, natural) is used to recapitulate the dynamics of ECM. Natural hydrogels such as collagen, gelatin methacrylate (GelMA), Matrigel, alginate, fibrin, and decellularized ECM (dECM) are widely used due to their inherent bioactivity and ability to support cell adhesion and proliferation.[4] Synthetic hydrogels, such as polyethylene glycol (PEG) and polyacrylamide, provide tunable stiffness and control over matrix composition, while semi-synthetic hybrids (e.g., PEG-GelMA, GelMA-dECM) combine biological cues with structural stability (Figure 1).[5]

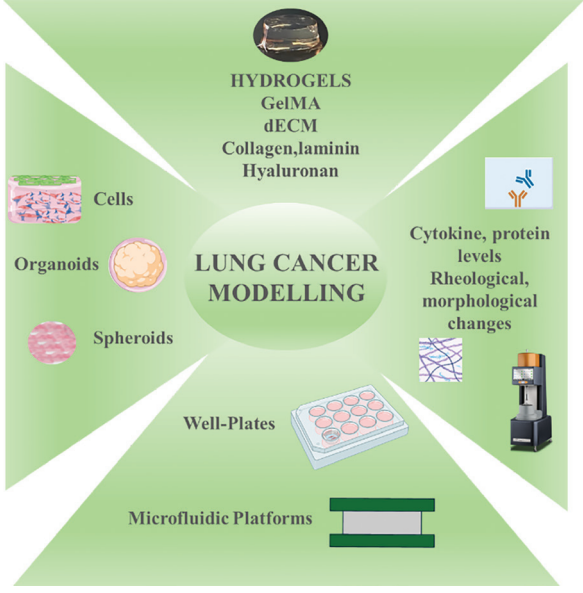


Figure 1. Schematic representation of hydrogel utilizattion in lung cancer modelling

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MATERIAL AND METHODS: Cancer cell lines A549 (adenocarcinoma), H1299 (non-small cell lung cancer), and H460 (large cell carcinoma) are frequently used in cancer modelling. Co-culture systems integrate fibroblasts, endothelial cells, and immune cells (e.g., macrophages) to simulate the TME and study cell-matrix-cell interactions. Patient-derived organoids preserve tumor heterogeneity, genetic mutations, and drug response profiles, representing a personalized *in vitro* cancer model. Tumor spheroids embedded in hydrogels recapitulate diffusion gradients and are used to evaluate drug penetration and metastasis. Further, they can be integrated into microfluidic platforms or well plates. As a next step, it is important to investigate ECM rheology, determine mechanical structure and cytokine expression levels, and further validate cell-matrix interactions.[6,7]

RESULTS: These models have shown that tumor cells embedded in hydrogels exhibit enhanced invasive behavior and increased expression of matrix metalloproteinases (enzymes responsible for ECM degradation and remodeling). From a biomechanical perspective, rheological analyses revealed that cancer-associated hydrogels typically exhibit higher storage modulus than healthy matrices, reflecting a stiffer microenvironment and increased collagen levels.[8]

CONCLUSION: Collectively, recent findings underscore the central role of the ECM and hydrogel-based systems in modeling lung cancer progression. The development of tissue-specific, mechanically tunable, and microfluidic-integrated hydrogels has transformed *in vitro* modeling from static 2D monolayers to dynamic, physiologically relevant 3D systems. Increased stiffness is now recognized as a key regulator of cancer cell fate, governing proliferation, EMT, and metastasis through mechanotransduction pathways such as YAP/TAZ and integrin–FAK signaling.[9] Despite significant progress, variability in dECM composition and crosslinking chemistry still challenges reproducibility and bioactivity. Moreover, current hydrogel-based models often lack immune cell components and vascular complexity, limiting their ability to fully emulate the native TME. Future efforts should integrate dECM-based hydrogels with organoid and microfluidic systems, supported by multi-omics profiling, to achieve patient-specific and physiologically relevant lung cancer models.

KEYWORDS: Organ-on-chip, biomaterial, hydrogel, extracellular matrix, tissue engineering, lung tumor-stroma interface

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