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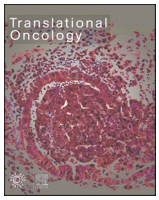

Perspective

Update on the relevance of mechanobiological mechanisms in lung cancer

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ABSTRACT

Lung tumorigenesis is characterized by mechanical perturbations at the molecular level that affect cancer development, progression and drug efficacy. Tumor expansion, alterations in the matrix stiffness and aberrant mechanical inputs lead to distorted mechanobiology of cancer and stromal cells. This dysregulation is accompanied by oncogenic mechanosignaling facilitating their invasion, migration and immune evasion. A growing volume of data highlight that such molecular events are translated to clinical phenotypes, which encompass a distinct group of oncogenic molecular mechanisms, prognostic and predictive biomarkers as well as putative therapeutic targets in lung cancer.

Mechanobiology is the scientific field which investigates the molecular and cellular processes that define the cell's response to mechanical cues. These cues are generated either from the cell's interior or the cell's adjacent microenvironment. It has been established that aberrant mechanical forces contribute to cancer development, progression, invasion, metastasis and drug response in solid tumors. Lung tissue is constantly subjected to mechanical stimulation during respiration and accumulating data reveal that mechano-induced molecular mechanisms are critical during all steps of lung tumorigenesis. Deregulated stiffness of the extracellular matrix (ECM), application of different types of mechanical forces, distorted mechanosignal transduction (mechanotransduction) of membrane receptors, derangement of the actin cytoskeleton and oncogenic activation of effector transcription factors characterize different subtypes of lung malignancies, thus providing novel biomarkers for therapeutic use (Fig. 1) [1].

Mechanical forces have been implicated even in the progression of early lesions in lung adenocarcinomas. Lung tumors develop under constant cyclic stretch from respiration. The mechanical strain triggers oncogenic processes, such as cell proliferation and migration, expression of ECM protein components and growth factors. Computational modelling of the mechanical alterations in the alveolar network demonstrates that the presence of early tumors augments the mechanical strain in the alveolar walls in close proximity to the tumor, whereas increased stiffness of advanced tumors seems to further augment the mechanical strain, an event that can promote progression of lung tumors to a greater extent [2]. Another type of mechanical stimulation that represents a potential mechanobiological biomarker is the level of interstitial fluid pressure (IFP). Following evaluation in lung cancer patients, IFP has been proven to be associated with clinicopathological characteristics including tumor size, advanced TNM stage, vessel and pleural invasion, as well as the expression of the Ki-67 proliferation marker (also known as marker of proliferation Kiel 67, MKI67). High IFP emerges as an independent prognostic factor in lung adenocarcinomas and correlates with worse response-free survival of these patients compared to patients with low IFP [3].

Regarding the role of the stromal protein components in lung cancer development, it seems that features of the tumor microenvironment (TME) that surrounds lung cancer cells form an intricate mechanobiological scenery that has been incriminated during lung cancer progression and metastasis. TME in non-small cell lung cancer (NSCLC) presents alterations in the architecture and composition of the ECM. Specifically, it exhibits a desmoplastic and fibrotic stroma enriched with cancer-associated fibroblasts (CAFs) in conjunction with exaggerated accumulation of fibrillar collagens. Changes in the expression, organization and topology of fibrillar collagens is linked to abnormal mechanotransduction that provides promising tumor-associated biomarkers with therapeutic potential. Anomalous fibrillar collagen deposition induces increased tumor stiffness and stiffness-associated molecular features in

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adenocarcinomas, such as the participation of yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) signaling, immune evasion, elevated activity of fibroblasts and vascular/lymphatic infiltration. Fiber density has been highlighted as an independent biomarker of poor prognosis in patients suffering from either adenocarcinomas or squamous cell carcinomas (SCC) [4].

There are several protein tools based on the plasma membrane that facilitate mechanotransduction. The main representatives are the mechano-induced ion channels, G protein-coupled receptors (GPCRs), cell adhesion molecules and receptor tyrosine kinases (RTKs) (Fig. 1). Among them, integrins constitute a notable family of mechanosensitive transmembrane receptors that modulate ECM remodelling and cell adhesion. Integrins are expressed in cancer cells and cells of the TME. They have been engaged in cancer cell proliferation, invasion, migration and tumorigenic processes involving the TME. Integrin subunit alpha 11 (ITGA11) in particular, has been found to contribute to NSCLC molecular pathology. ITGA11 is a receptor of fibrillar collagen and it is highly expressed in NSCLC-associated fibroblasts. ITGA11 induces TME stiffness, whereas deficiency of integrin α11 reduces tumor growth in A549 tumor xenografts. Loss of stromal integrin α11 expression is associated with decreased collagen stiffness and inhibition of the metastatic potential, therefore integrin α11 seems to foster lung cancer tumorigenicity via collagen stiffness of the tumor stroma [5].

Mechanical stresses can be either transmitted to or generated within the cell's cytoplasm. Consequently, additional candidate mechanosensitive molecules involved in the remodelling of actin cytoskeleton characterize the mechanobiology of metastatic lung cancer cells. Myosin heavy chain 9 (MYH9) is a protein of the myosin superfamily implicated in cytoskeletal reorganization, cellular pseudopodia formation, and migration. It is highly expressed in NSCLC and has been highlighted as an independent prognostic factor in patients with resectable NSCLC that show poor prognosis and belong to TNM stages I to III [6]. Ezrin, a member of the ezrin, radixin and moesin (ERM) protein family that links F-actin to the cell membrane, mediates mechanotransduction in lung cancer cells. Ezrin modulates the oncogenic process in accordance with the applied mechanical tension and is correlated with aggressive phenotypes in lung cancer [7,8]. An additional actin-binding protein, actinin alpha 4 (ACTN4), is highly expressed in actin-rich protrusions and invadopodias being associated with survival in patients suffering from lung adenocarcinomas [9].

Ultimately, aberrant mechanobiology in the course of lung cancer progression is integrated at the transcriptional level. Decisive mechano-induced transcriptional cofactors are the YAP and TAZ coactivator proteins. YAP and TAZ are central effectors of the highly conserved Hippo signaling axis, which is potentiated by stress and mechanical signals, cell polarity, cell-to-cell interactions, ECM and intracellular tension. During dysregulation of the Hippo signaling pathway in lung cancer cells, YAP/TAZ translocate to the nucleus and interact with the transcriptional-enhanced associate domain (TEAD) family of transcription factors to regulate gene expression (Fig. 1). YAP/TAZ have been implicated in molecular mechanisms of aggressive properties in NSCLC, such as resistance to administered drugs, particularly chemotherapy, mitogen-activated protein kinase (MAPK) and epidermal growth factor receptor (EGFR) targeting, immune evasion of tumor cells and features of metastasis like epithelial-to-mesenchymal transition (EMT) [10]. There are rare YAP/TAZ activating mutations, yet gene amplification and hindered degradation frequently cause dysregulation in lung cancer cells. In addition, genetic alterations are also presented with the formation of protein fusions. YAP or TAZ serve as one part of the hybrid protein which can hyperactivate a TEAD transcription factor-based transcriptome [11]. Three cases with clear cell stromal tumor of the lung have been described harboring *YAP-transcription factor E3* (*TFE3*)

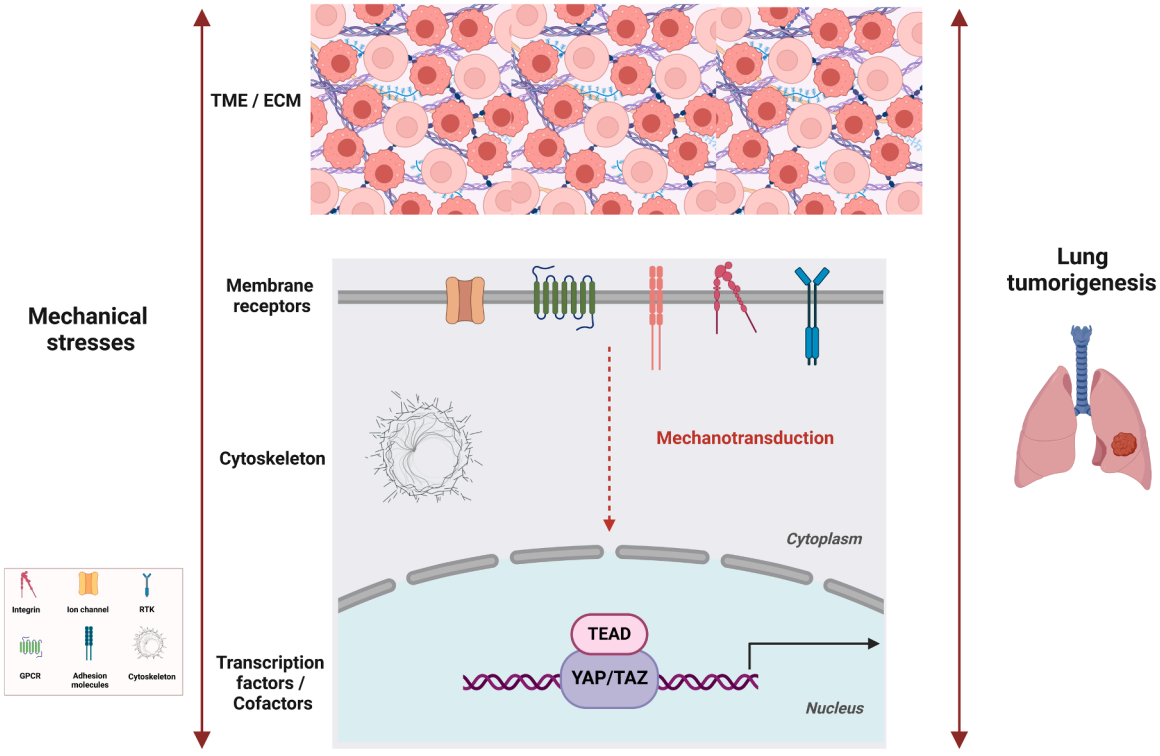

Fig. 1. Aspects of mechanobiology in lung cancer. Mechanical stresses (compression, tension, stretch, matrix stiffness, interstitial fluid pressure) affect the molecular cascades of lung cancer cell tumorigenesis throughout the TME and ECM, mechanosensitive membrane receptors, cytoskeletal rearrangements and mechano-induced oncogenic transcription. ECM, extracellular matrix; GPCR, G protein-coupled receptor; RTK, receptor tyrosine kinase; TAZ, transcriptional coactivator with PDZ-binding motif; TEAD, transcriptional-enhanced associate domain transcription factors; TME, tumor microenvironment; YAP, yes-associated protein. Created with BioRender.com (modified from Fig. 1 in Ref. [14] (article licensed under a Creative Commons Attribution 4.0 International License; https://creativecommons.org/licenses/by/4.0/)).

gene fusions [12]. Components of the Hippo signaling pathway crosstalk with other oncogenic factors such as mutated EGFR, $BRAF^{V600E}$ and $KRAS^{G12C}$; this suppresses efficient response of lung tumor cells to several tyrosine kinase inhibitors (TKIs), while YAP/TAZ/TEAD selective targeting with small-molecule compounds seems to restore sensitivity to the administered drugs [10]. YAP/TAZ are also associated with the regulation of innate and adaptive immunity against malignant cells, thereby affecting response to the otherwise favourable immunotherapy for lung cancer [10].

Studies that further evaluate YAP/TAZ/TEAD targeting in combination with drugs that are already in use are still limited. Although YAP/TAZ/TEAD modulation seems to be a promising target to overcome drug resistance, they demonstrate a complex and controversial role. YAP and TAZ function as molecular switches and become either activated or suppressed depending on the preclinical and clinical settings. Therefore, targeting requires fine-tunned modulation and not simply blockade of the pathway. Furthermore, the fact that the activation of the pathway occurs via dephosphorylation rather than phosphorylation makes standard pharmacological approaches counterproductive. In this context, there are alternative ways to efficiently repress oncogenic activity of the Hippo signaling pathway, such as abrogation of protein-protein interactions and novel methods like PROteolysis Targeting Chimera (PROTAC) techniques for manipulation of the target protein [13].

Notwithstanding that several mechanobiological markers and therapeutic targets emerge along the molecular cascades that mediate aberrant mechanical stimulation in lung cancer cells, notable issues are raised that remain to be addressed for achieving efficient therapeutic exploitation of this rapidly evolving field. These issues include the fact that the complex interactions and molecular crosstalk underlying mechanobiology in lung tumorigenesis are still unclear. Furthermore, it is critical to establish a sparse, reliable set of biomarkers to screen suitable patients across the entire disease process, for mechanobiology targeting. An additional aspect is the identification of therapeutic approaches that avail mechanical properties for selective drug delivery. Nevertheless, mechanobiology seems to offer promising targets to design novel drug combinations aiming to overcome resistance to current treatment regimens.

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CRediT authorship contribution statement

Antonios N. Gargalionis: Writing – original draft, Visualization, Conceptualization. **Kostas A. Papavassiliou:** Writing – original draft, Visualization, Conceptualization. **Efthimia K. Basdra:** Writing – review & editing, Conceptualization. **Athanasios G. Papavassiliou:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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