Review Article

Mechanical stretch modulates cell migration in the lungs

Cecilia López-Martínez[1,2], Covadonga Huidobro[2], Guillermo M. Albaiceta[1,2,3], Inés López-Alonso[2]

[1]Departamento de Biología Funcional, Instituto Universitario de Oncología del Principado de Asturias, Universidad de Oviedo, Oviedo, Spain; [2]Instituto de Investigación Sanitaria del Principado de Asturias, Oviedo, Spain; [3]Unidad de Cuidados Intensivos Cardiológicos, Hospital Universitario Central de Asturias, Oviedo, Spain

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Correspondence to: Inés López-Alonso. Laboratorio de Investigación Traslacional del Paciente Crítico, Instituto de Investigación Sanitaria del Principado de Asturias, Avenida de Roma s/n, 33011 Oviedo, Spain. Email: ila@lab14.org.

Abstract: Cell migration is a core process to preserve homeostasis. Release of chemotactic signals induces changes in cell cytoskeleton to facilitate migration. This includes the rearrangement of cytoskeleton, genomic reprogramming and the modification of the surrounding extracellular matrix (ECM) to allow the motion of cells through. In the special case of repair after acute lung injury, cells must migrate while exposed to an increased mechanical stretch caused either by an increased work of breathing or positive-pressure ventilation. Interestingly, the cell response to this increased mechanical load can modify virtually all the mechanisms involved in cell migration. In this review we explore the interplay between stretch and the machinery responsible for cell migration. A translational approach to find new therapies in acute lung injury must take into account these interactions in order to develop effective treatments that promote lung repair.

Keywords: Lung repair; mechanical stretch; cell migration; acute lung injury

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Introduction

Cell migration is an essential process during organ development, growth and tissue repair (1). To be effective, migration must be a carefully orchestrated phenomenon that involves cell signaling, remodeling of the extracellular matrix (ECM) to allow the passage of cells, motion of cells and engraftment in a new niche. Moreover, this process has consequences not only on the behavior of the migrating cell, but also in its environment. There is a large variety of molecular mechanisms behind these processes, including receptor activation, changes in the proteins of the cytoskeleton, release of mediators, genetic reprogramming and activation of transcription factors (2). In the special case of acute lung injury, cell migration plays key roles from the onset of the initial damage to the final steps of tissue repair (3).

Moreover, the lungs are submitted to a continuous mechanical stress during ventilation. Although the magnitude of the forces and their distribution during spontaneous breathing are well tolerated, the excessive mechanical stretch during positive-pressure ventilation is a pathogenetic factor leading to the so-called ventilator-induced lung injury (VILI) (4). There is emerging evidence that some of the molecular mechanisms responsible for migration can be modulated by mechanical stretch. As avoidance of VILI or induction of tolerance to mechanical stretch helps to limit additional injury to the lungs and may improve the outcomes in ventilated patients (5), understanding these mechanisms is essential to develop effective cell-targeted or cell-based strategies to promote tissue healing.

An overview of cell migration

Efficient cell migration behavior implies not only physical and chemical crosstalk within the population

of migrating cells, but also some sort of communication mediated by diffusible factors and the ECM where cells are embedded. Both intrinsic and extrinsic variables are integrated to achieve a common goal: a combination of actin polymerization and actomyosin contraction which eventually leads to cytoskeleton rearrangement, structural reorganization and morphological polarization.

Chemotaxis

Cell migration is driven by gradients of biochemical signals, released from the sites of injury. These molecules bind to specific receptors triggering intracellular responses. Most soluble factors, including chemokines and growth factors, induce CDC42 and RAC activation to promote actin polymerization, leading to cell polarization and protrusion formation. In neutrophils, phosphoinositide 3-kinase (PI3K) activity increases phosphatidylinositol 3,4,5-triphosphate [PtdIns(3,4,5)P_3] levels at the front. This generates binding sites for PH domain-containing proteins, like activators of the RAC, leading to actin polymerization and protrusion (6).

Moreover, chemotactic factors are responsible for the activation of transcriptional programs that define the migration phenotype. For instance, local production of the cytokine UPD activates the JAK-STAT pathway in nearby cells. In particular, UPD binds to a transmembrane receptor, activating the tyrosine kinase JAK which phosphorylates both itself and the UPD receptor. This enables STAT binding to the receptor complex, and its phosphorylation. Ultimately, phosphorylated STAT dimerizes and translocates to the nucleus to activate transcription and promote cell motility. Mutations affecting any component of the JAK-STAT pathway disrupt cell migration (7).

Cellular changes

Different pathways orchestrate the polarization of cells during migration at two levels. Firstly, a polarity axis emerges, allowing to distinguish the front from the rear. At the front, actin polymerization leads to the formation of membrane protrusions, filopodia and lamellipodia. This cytoskeletal rearrangement is generally induced by RAC and CDC42. At the rear, the RHO family of small GTPases mediates actomyosin contraction. Release of cell-to-ECM adhesions is further required to enable cell movement (8). Secondly, and considering migration as a collective event, cells are divided into two categories, depending on their relative location within the cell cluster. Leader cells at the front of the migratory mass determine the direction and speed of the migration. Precisely because of their peripheral location, leader cells are more expose to external agents, like chemoattractants, and exert an essential role in ECM remodeling. Follower cells, behind the leaders, strongly depend on cell-to-cell adhesion mediated by cadherins and can influence leaders behavior (9).

Changes in the ECM

As cells must migrate through the ECM, the physical properties of the latter notably influence the migratory strategy. Cells can use both proteolytic and non-proteolytic mechanisms for ECM processing. As stiffness increases, cells experience deformation that can induce conformational changes within the adhesion complexes. Focal adhesions mediate the interaction of cells with the ECM through integrins, a family of transmembrane proteins, and cytosolic proteins like actin fibers. Under forces, the adhesion complex adaptor protein CRK-associated substrate leads to exposure of phosphorylation sites for the SRC-family kinases which recruit other proteins to downregulate RAC1 and repressor/activator protein 1 (RAP1) homologue activity (10). Also, increased activity of SRC-family kinases is linked to ECM degradation through increased expression of matrix metalloproteinases (MMPs) to favor movement (11). In addition, other secreted ECM components modify its own composition and the nature of the engaged integrins.

Impact of stretch on cell migration

The lung parenchyma is submitted to mechanical stress in each breath. During acute lung injury, the increased work of breathing or the need for mechanical, positive-pressure ventilation can increase this mechanical load beyond the tolerance limits. This stretch modifies cell and matrix behavior, and all the processes related to migration can be affected.

Chemotaxis

Mechanical ventilation can trigger a mechanotransduction response in response to positive transpulmonary pressures, thus leading to the secretion of different active molecules that are involved in cell recruitment. The secretion of these chemoattractants in response to stretch by the lung parenchyma cells can result in a more severe lung injury developing biotrauma (12).

Mostly inflammatory related, the balance in the release of pro- and anti-inflammatory cytokines directs the immune response, with IL-8 (MIP-2 in rodents) playing a central role as one of the most potent leucocyte chemoattractants. Additionally, pro-inflammatory cytokines like TNF-α or IL-1, induce NF-kB activation, a main step in the transcription of genes involve in the innate immune response. As part of this response, adhesion molecules are expressed in the endothelium, which results in the extravasation of polymorphonuclear leucocytes and other immune cells few minutes after mechanical stimulus starts (13). Overall, neutrophilic infiltration is facilitated by mechanical stretch.

Fibroproliferation, once believed a late phenomenon, starts early as an attempt to form a collagen scar. In this context, pulmonary fibroblasts migrate to the damaged area, proliferate and secrete epithelial growth factors, which promote migration and proliferation (14), and deposition of components of the basement membrane (15). Moreover, these fibroblasts control the epithelial repopulation after injury through direct contact or by means of secreted factors (16).

Cellular changes

External mechanical forces can drive changes in cell shape, mediated by remodeling of the cytoskeleton under the cell membrane. The mechanical insult is sensed by several cell surface adhesion receptors, such as integrins and cadherins. Integrins bind to ECM or focal adhesions while cadherins attach to the surrounding cells (17). These molecules bind to other cytoplasmic proteins such as talin or vinculin creating a filament network with F-actin. In response to a mechanical stimulus, actin filaments suffer important rearrangements, small GTPase RhoA is activated which in turn activates myosin II that is present in junctions cell-cell. It is well known that in this context vinculin can bind to an actin nucleation factor that attaches to the sides of actin filaments and favours the building of a framework structure (18). In addition HGF secreted by fibroblast can activate specific receptors in epithelial cells increasing vinculin levels favoring spreading and migration through Rac activation (19).

The mechanical stimulus also reaches the nucleus. There is a protein complex responsible for connect cytoplasm and nucleus, known as LINC complex (linker of nucleoskeleton and cytoskeleton) and contains among others nesprins, sun and lamins (20). Lamins are intermediate filament-like proteins that form a molecular scaffold on the nucleoplasmic side of the inner nuclear membrane anchoring to this and to peripheral DNA and chromatin (21). As a consequence of mechanical stress, lamins and the nuclear scaffold rearrange and modify nuclear organization and gene expression, promoting expression of a proliferation gene signature and epithelial proliferation through FAK-dependent (Ras pathway-mediated) ERK activation (22).

ECM remodeling

The ECM plays a key role in cell migration. Damage in the ECM due to mechanical ventilation may be caused directly by the stretch and strain forces or by the inflammatory reaction produced by mechanotransduction of the stimuli by surrounding cells. This will alter the physical properties of the ECM, thus modifying cells ability to migrate.

This scaffold is composed of macromolecules such as collagen, elastin, hyaluronan (the most common glycosaminoglycan) and proteoglycans that are responsible for the flexibility, mechanical strength and water content of the lung parenchyma. These components can interact with different elements, influencing cell proliferation, matrix deposition and inflammatory response.

The turnover of matrix macromolecules is controlled by MMPs, a family of zinc-containing endopeptidases that degrade the different components of the ECM. They are classified, according to their substrate, as gelatinases (MMP-2 and 9), stromelysins (MMP-3, -10 and -11), collagenases (MMP-1, -8 and -13), matrilysins (MMP-7 and -26) and membrane MMPs (MMP-14, -15, -16, -17, -24 and -25). These enzymes can also interact with other molecules such as inflammatory mediators, growth factors or membrane receptors, regulating cell-cell and cell-matrix interactions (23).

Changes in the balance between deposition and turnover of the different components will modify the mechanical properties of the matrix, which can lead to injury and eventually severe lung disease.

Mechanical ventilation leads to damage in the ECM: initially, stretch and strain forces causes fragmentation of the glycosaminoglycans, leading to distortion of the scaffold structure and eventually edema (24). Later, different types of MMPs are released and activated, which can have opposing functions. For example, MMP-9 degrades collagen IV, which further disrupts the matrix, but it is also associated with liberation and activation of protective cytokines (25). In opposite, MMP-8 promotes acute inflammation, but also its resolution in a later stage (26,27). This shows the complex relation between lung injury and MMP activation.

Once the mechanical damage stops, the wound healing process begins. This is characterised by an excessive deposition of the components of the matrix, specially type I collagen, which increases matrix stiffness. The stiffened scaffold enhances resident cells migration and exogenous cells invasion towards the damaged zones. This behaviour is mediated mainly by integrins, which sense variations in the stiffness and induce remodelling of the cytoskeleton, generation of invadosomes and lamellae, and MMPs production, changes that increase de migratory phenotype (28).

Clinical implications

Basic, translational and clinical research have helped to identify a variety of pathogenetic mechanisms that lead to lung injury. Unfortunately, many of them are core homeostatic processes, so that any intervention aimed to modulate them may lead to a large number of adverse effects and unwarranted consequences. Moreover, mechanical stretch, if excessive, may promote further damage, triggered by the very same biochemical routes. With this in mind, it is easy to explain the lack of translation of the majority of the research in the field. For instance, acute inflammation may contribute to lung injury, but anti-inflammatory or immunosuppressive drugs may further interfere with repair (29).

In opposite, enhancement of repair may represent a novel, safer approach. The mechanisms underlying lung repair are only partially known, but cell migration is a key process in all of them (3). As the majority of the cases of acute lung injury in which repair may be relevant are submitted to mechanical ventilation, understanding the interaction between stretch and cell migration is of paramount importance to improve the outcomes of these patients. Moreover, the increased availability of extracorporeal gas exchange devices allows the clinicians to limit or even completely abolish lung stretch with preservation oxygenation and CO_2 removal, but the optimal settings are still unknown (30).

There are several strategies to manipulate cell migration. Regarding chemotaxis, blockade of the recruitment of inflammatory cells have been extensively studied (31-33). Avoidance of neutrophilic infiltration decreases lung damage in the majority of experimental models using chemokine antagonists. However, the risk of immunosuppression limits its application in patients. Moreover, there is emerging evidence that neutrophils may be essential for later repair, thus limiting the usefulness of these therapies (34,35). Targeting of cell machinery responsible for migration has been also tested, mainly using growth factors such as KGF (36). Again, the positive results in experimental studies have not been translated to the clinical practice (37).

Finally, ECM remodeling has been aimed by different therapies. Similarly to manipulation of the inflammatory response, the use of MMP inhibitors has been protective against lung injury in experimental models of acute injury (27,38). However, some of these enzymes are required for modulation of the inflammatory response or later repair (39), and their absence has been related to worse outcomes.

Conclusions

The dual role of the majority of the responses during acute lung injury difficulties the translation of the experimental findings to the clinical practice. Blockade of early pathogenetic responses may impair the healing process and, in opposite, early promotion of cell migration can cause further damage to the lung parenchyma. In this complex scenario, identification of specific pathways with single effects seems an extremely difficult challenge. Therefore, deep knowledge of the underlying mechanisms, in complex, clinically relevant experimental models, and precise timing of the interventions are required before reaching the goal of an effective therapy to change the clinical course of acute lung injury.

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Footnote

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