Intermediate filaments against actomyosin: the david and goliath of cell migration

Emma J van Bodegraven, Sandrine Etienne-Manneville

Intermediate filaments against acto-myosin: the David and Goliath of cell migration

Emma J. van Bodegraven, Sandrine Etienne-Manneville*

Cell Polarity, Migration and Cancer Unit, Institut Pasteur, UMR3691 CNRS, Equipe Labellisée Ligue Contre le Cancer, F-75015, Paris, France.

*Correspondence: setienne@pasteur.fr

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Abstract

Intermediate filaments (IFs), together with actin and microtubules, constitute the cytoskeleton and regulate essential biological processes including cell migration. Despite the well-described changes in the composition of IFs in migrating cells, the mechanism by which these changes may contribute to cell migration remains elusive. Recent studies show that IFs control cell migration by impacting the acto-myosin machinery. This review discusses how the unique physical properties of IFs, the interplay between IFs and the acto-myosin network, and the connection of IFs with cell adhesive structures participate in cell migration. We highlight the biochemical and mechanical mechanisms by which IFs control acto-myosin generated forces to influence migration speed and contribute to nuclear integrity and cell resilience to compressive forces in 2D, as well as in confined 3D migration.

Introduction

Intermediate filaments (IFs) are 10 nm diameter filaments composed of homo- or heteropolymers of IF proteins which are encoded by a large family of 70 different genes. They extend throughout the cytoplasm, connect cortical cell structures to intracellular organelles such as the nucleus, and are involved in a wide range of biological processes [1–3] including cell migration [4–7].

Most in-depth studies on cell migration have focused on the actin cytoskeleton. These studies have highlighted the key role of actin in generating forces that are essential for cell migration [8,9]. Actin polymerization and actomyosin contraction regulate the formation of protrusions, traction forces and rear retraction and enable forward cell movement. The multiple and essential mechanical functions of the acto-myosin network as well as its recently demonstrated ability to adjust to the

physical properties of the microenvironment [10] have pointed to the actin cytoskeleton as a mastermind of cell migration. However, evidence for the rearrangement of the microtubule and IF network during migration have progressively emerged, suggesting that the three cytoskeletal structures cooperate to control cell migration [4,5,11,12]. The engagement of microtubules in mesenchymal migration has been proven by their contribution to cell polarization, formation of cell protrusions, and the turnover of focal adhesions (FAs) [12–15]. The role of IFs in cell migration has long remained elusive despite well-described changes in IF expression that contribute to cell migratory properties [6]. The best example is the upregulation of vimentin upon epithelial-to-mesenchymal transition (EMT) [16,17]. Accordingly, many different studies have indicated that cell migration is impacted by the loss of IFs although the net effect on migration depends on the cell and IF protein types [5,18–22]. The dynamic regulation of IFs is still poorly understood and the major question that remains is how IFs, despite lacking molecular motors and not being intrinsically polarized, participate in cell migration.

IFs may impact cell migration through their interaction with actin and microtubules via cytoskeletal linker-proteins such as plectin and Adenomatous Polyposis Coli (APC) [23–30]. Alternatively, IFs can serve as a platform for signaling pathways that are important for cell migration [4,31]. Finally, IF-influence on cell migration may involve their unique physical properties. Following these hypotheses, the impact of IFs on cell mechanics and on the acto-myosin machinery has gained in-depth attention over the recent years. This review will highlight the intrinsic mechanical properties of IFs and their dynamic interplay between the acto-myosin machinery and the IF network. It will discuss how the mechanical and signaling properties of IFs enable them to control the amplitude and the distribution of forces during migration and provide resistance to compressive forces in a confined 3D environment.

IFs impact cell mechanical properties

Compared to actin and microtubules, single IFs are extremely resistant to breakage, can be stretched more than 3-fold [32,33], and have been shown to undergo strain-stiffening [34,35]. Force-strain curves obtained from optically trapped filaments show a steep linear increase in filament stiffness at low strains, which is attributed to the elastic stretching of α-helices. Then, the force remains equal while strain increases. The uncoiling of α-helices into β-sheets is thought to be responsible for this observation which reflects the ability of IFs to absorb energy [34,35]. Single vimentin filaments are able to dissipate more then 70% of the input energy as measured by the cyclic stretching and relaxation of filaments [36]. At large strains, a strong increase in stiffening is observed which is likely to result from increased pulling on the β-sheets [34,35]. Vimentin networks also display elastic and strain-stiffening properties [37]. Compared to actin, vimentin networks are highly elastic. However, their elasticity

decreases when actin is mixed in the composite network. At low strains, the actin network stiffens while vimentin softens, attributed to slippage of polymers. At high strains when the actin network softens due to fluidization, the vimentin network stiffens by the unfolding of filaments [37]. In cells, IF's mechanical characteristics have shown to contribute to the cells ability to withstand large deformations [38] and propagate local deformations throughout the cytoplasm to prevent damage [39]. During cell migration, these physical properties of IFs may allow them to take up the energy generated by actomyosin-generated forces.

IFs tame the force-generating acto-myosin machinery

There are several ways by which the acto-myosin cytoskeleton affects the composition of the IF network [4]. For example, decreasing acto-myosin contractility decreases keratin IF node dynamics in SW13 cells [40] and keratin localizes towards cell-cell adhesions of embryonic mesendoderm cells upon the application of local tensions [41]. In addition, the solubility of vimentin, indicative of filament disassembly, is increased in human mesenchymal stem cells on soft substrates compared to stiff substrates and upon inhibition of acto-myosin assembly [42]. Conversely, although the exact mechanism often remains ~~often~~ unknown, changes in the IF network influence cellular forces and the force-generating capacity of the acto-myosin machinery [19,22,43–45]. IFs direct- or indirectly interact with actin via cytoskeletal linkers such as plectins [23–26,26–28,46,47] and modulate RhoA activity, a RhoGTPase which directly promotes the formation of acto-myosin stress fibers and cell contractility. In osteosarcoma cells, vimentin IFs inhibit RhoA by binding to the guanine-exchange-factor GEF-H1 [48] and in MDCK cells, keratin 18 activates RhoA via another RhoA-GEF, i.e. Solo [49].

During collective migration of cell sheets two different types of actin fibers are observed; longitudinal stress fibers which are anchored at FAs at the front of leader cells and extend towards the rear of the cell and interjunctional transverse arcs anchored at adherens junctions (AJs) which connect the lateral sides of adjacent cells. These structures are engaged in a continuous retrograde flow, organized by the movement of myosin motors along stress fibers [50–52]. High traction forces are generated at the front of leader cells. These forces contribute to the migration of leaders and are transmitted to follower cells by adherens junctions [53–56]. Two recent studies indicate that during collective cell migration IFs influence the generation and the distribution of forces by the direct or indirect interaction with the acto-myosin machinery (Figure 1).

In collectively migrating astrocytes depletion of vimentin, glial fibrillary acidic protein (GFAP), and nestin decreases migration speed, persistence, and directionality [57], accompanied by a drastic change in the actin organization (Figure 1A). In IF-depleted cells, longitudinal stress fibers are more

pronounced and interjunctional transverse arcs are rarely observed. In parallel, the amplitude and distribution of traction forces is altered. Instead of concentrated forces at the cell front, traction forces are exerted through FAs at the front, center, and back of IF-depleted cells. Moreover, depletion of IF proteins increases traction forces in follower cells resulting in similar traction forces exerted by leader and follower cells [57]. Overall, the loss of IFs increases forces throughout the migrating monolayer. Plectin depletion mimics the migratory phenotype of IF depleted astrocytes, supporting the hypothesis that IFs regulate cell migration and traction forces through an interaction with the acto-myosin force generating machinery [57].

An interaction of keratin 6 with myosin IIA, the molecular motor responsible for acto-myosin contractility, has been described in collectively migrating keratinocytes (Figure 1B). Keratin 6a and 6b (K6a/b) null mice show impaired epithelization and blistering [58] and in keratinocyte explants of K6a/b null mice cell migration upon skin injury is enhanced [59]. This suggests that the upregulation of K6a/b, which is normally observed following skin injury, attenuates keratinocyte migration. The attenuation of migration is needed to ensure collective keratinocyte migration and re-epithelization. The impact of K6a/b on collective migration may be attributed to the direct interaction of K6a/b with myosin IIA [60]. In migrating K6a/b null keratinocytes, myosin IIA protein, but not mRNA, levels are decreased indicating that the keratin-myosin IIA interaction stabilizes myosin IIA to increase traction forces and slow down migration. Accordingly, larger FAs with a lower turnover are observed in K6a/b expressing cells [60]. However, the role of myosin IIA in keratinocyte migration is complex. Depleting myosin IIA does not affect keratinocyte migration, possibly due to a redundancy of other myosin isoforms. In fact, different pharmacological inhibitors that affect all myosin II isoforms, ML-7 (a myosin light chain kinase inhibitor) and blebbistatin (inhibitor of myosin II ATPase activity), have different effects on wild type and K6a/b null keratinocytes. As blebbistatin is able to solely inhibit migration of K6a/b null keratinocytes without affecting wild type cells, the enhanced migration potential is thought to depend on myosin II ATPase activity and increased contractility [60]. Together, results from these recent studies suggest that IFs regulate acto-myosin generated forces to optimize, i.e. promote or attenuate, collective migration by interacting with and modulating the force-generating machinery.

IFs ~~over~~ control cell adhesions

The actin cytoskeleton connects to adhesive structures, such as integrin-based FAs and cadherin-based AJs. FAs and AJs are regulated by acto-myosin cables that directly connect to these structures [61,62]. For instance, the association of stress fibers and increase ind~~d~~ acto-myosin contractility promote FA maturation and regulate FA turnover [63]. Accordingly, tension-dependent FA maturation, strength, size and turnover as well as changes in the dynamics of AJs may be regulated by the IF network through their influence on acto-myosin contractility [4,6,47,64–67] (Figure 2). It is

tempting to speculate that the loss of interjunctional actin arcs following depletion of vimentin, nestin and GFAP in astrocytes ~~may be~~is responsible for AJ alterations observed in these cells as well [57].

However, adhesion molecules (integrins or cadherins) are engaged in intracellular signaling pathways that conversely regulate the actin-myosin network. This regulation enables the cell to adapt to the biochemical and mechanical properties of the environment of the cell. Thus, IFs can also modulate acto-myosin contractility via their interaction with adhesive structures (Figure 2). IFs interact with FAs via plectin (see [6], [23],[65] for detailed reviews on this interaction) (Figure 2B). Vimentin directly binds the tail of β_3- [68] and $\alpha_2\beta_1$-integrins [69] (Figure 2B), and GFAP and vimentin interact with adhesion molecules such as vinculin and talin [57] (Figure 1A). In addition, IFs regulate the clustering and dynamics of integrins and the recruitment and activity of adhesion molecules involved in intracellular signaling, i.e. focal adhesion kinase (FAK) [47,68,70–74] (Figure 2B). These ~~the~~ interactions of IFs with FAs can directly impact ~~actin and~~ signaling pathways and actin to regulate cell migration. Despite limited evidence, IFs might similarly affect the acto-myosin network by interacting with AJs.

The effect~~s~~ of IFs on FAs and AJs can also involve other integrin- and cadherin mediated adhesive structures to which IFs connect, hemidesmosomes and desmosomes. These epithelial structures are important to withstand mechanical stress and tension [4] (Figure 2A). Deletion of plectin, which disrupts the connection of IFs to hemidesmosomes, increases FAs and actin filaments [65,75]. This interplay between hemidesmosomal cell-matrix adhesions and FAs has recently been described in more detail in migrating keratinocytes [76] where keratin regulates the formation and localization of hemidesmosomes to attenuate cell migration and optimize re-epithelization [18]. In migrating keratinocytes, hemidesmosomes are distributed over the entire cell basal surface and are slightly enriched at the cell-border of leader cells in close proximity to FAs [76] (Figure 2A). Here, the hemidesmosomal components plectin and β_4-integrin align with keratin filaments in linear arrays. Disruption of these arrays following β_4-integrin depletion prevents hemidesmosome formation and promotes maturation of FAs, acto-myosin contraction, and traction forces. Expression of β_4-integrin mutants and treatment with integrin-blocking antibodies have the same effect suggesting that the connection of β_4-integrins with the ECM and the IF network are both necessary for hemidesmosomes to control FA maturation [76]. The linear alignment of IFs in hemidesmosomes adjacent to FAs indicates that IFs are stretched and have taken up the energy generated by ~~the uptake of energy by IFs which are stretched in response to~~ acto-myosin contractility. High linear keratins indeed correspond to the uptake of energy as has been shown by laser ablation of linear keratins in stretched cells [38]. Laser ablation of keratin in stretched cells leads to the rapid increase in the cell area which can be interpreted as a loss in tension and the release of energy [38]. Therefore, the ability of

hemidesmosomes to reduce cell contractility and traction forces at FAs is likely to be achieved by the unique physical properties of IFs. Migration of the monolayer requires the disassembly of hemidesmosomes in leader cells. This results in a lower number of hemidesmosomes in leader cells compared to the trailing area of the migrating monolayer [76,77]; this may account for a balanced generation of traction forces to optimize migration. In tumor cells, the composition of hemidesmosomes is frequently altered [78]. This ~~may~~ could result in an imbalance of traction forces ~~that could~~and be responsible for the inappropriate migratory behavior observed during EMT.

In epithelial lung cancer cells, vimentin and keratin are observed in close proximity to β_4-integrin-containing cell-matrix adhesions, reminiscent of hemidesmosomes (Figure 2B). Vimentin organizes in arrays near these adhesions [79], interacts with β_4-integrin via plectin [80] and increases the life-time of β_4-integrin puncta [79]. The~~is~~ interaction between β_4-integrin-containing adhesions and vimentin regulates Rac1 activity and recruitment to promote actin polymerization and directed cell migration [79]. This recent study supports the hypothesis that IFs regulate intracellular signaling at cell adhesions to control actin dynamics and cell migration.

IFs can also influence cellular forces via desmosomes [4,81–83]. IFs are tightly tethered to desmosomes mediated by desmoplakin which is important to maintain keratinocyte sheet integrity. During wound healing, desmosomes must progressively disassemble to enable cell migration and reform afterwards upon re-epithelization. Depletion of K6a~~/K6~~b disrupts desmosomes and increases the speed of migrating keratinocytes. This alters re-epithelization and renders the epithelial cell sheet fragile [60]. The increase in migration speed can be partially rescued by the overexpression of desmoplakin in K6a/b null keratinocytes. Desmoplakin overexpression may recruit other keratin proteins expressed in these cells and stabilize desmosomes. This suggests that IF-connected desmosomes are important to attenuate migration and optimize re-epithelization. As myosin IIA depletion has the same effect on cell-cell adhesions as the loss of K6a/~~K6~~b, the previously mentioned interaction between keratin 6 and myosin IIA might be key to this coordination. Keratin filaments may thus promote efficient wound closure through their interaction with myosin and the regulation of the actin cytoskeleton. Regardless of the contribution of other keratins, ~~T~~the upregulation of K6a/K6b following injury seems essential to coordinate collective keratinocyte migration by stabilizing FAs and desmosome-mediated cell-cell adhesions (Figure 1B).

IFs alleviate compressional forces exerted on the nucleus

In most physiological conditions, cells migrate in a 3D environment and must navigate through tight constricted spaces. Cortical actin and microtubules align along substrate tracks and enhance migration speed when confinement, up to a threshold, is increased [84,85]. In contrast, recent studies show that

vimentin attenuates the migration of cells through confined spaces and prevents the confinement-induced increase in migration speed [85,86]. In the absence of vimentin, increased confinement promotes migration speed in an actin and microtubule-dependent manner [85]. This suggests that vimentin counteracts the influence of actin and microtubules during confined migration [85]. As cells migrate through narrow spaces, the cells and their nuclei are subjected to compressive forces from surrounding tissues and vimentin is thought to have a protective role in this process (Figure 3). Classically, the nuclear lamina composed of lamin A/C and lamin B1 control~~s~~ nuclear stiffness and protect the nucleus from damage [87]. However, the cytoplasmic vimentin IFs are needed for the stiff elastic response of the nucleus and thereby contribute to the mechanical homeostasis of the nucleus during confined migration [88]. Recent evidence shows that vimentin IFs organize into a cytoplasmic nuclear cage to protect the nucleus against compressive forces [86]. Depletion of vimentin in mouse embryonic fibroblasts (MEFs) leads to smaller and rounder nuclei with increased contour fluctuations. These fluctuations are indicative of decreased nuclear tension, which is supported by decreased cellular stiffness in regions above the nucleus [85,86]. Therefore, the ability of vimentin depleted cells to move faster through confined spaces might result from ~~an~~ increased deformability of the nucleus. However, this occurs at the cost of increased DNA damage and necrosis as cells migrate through confined spaces (Figure 3), which is also observed upon axial compression in collagen gels [86]. The data suggest that vimentin has a primary role in maintaining nuclear integrity during confined migration by counteracting the strong actin-generated forces which tend to increase migration speed. This protective function of vimentin IFs may be related to their above-mentioned physical properties ~~stiff elastic properties as observed in reconstituted IF networks.~~ The ~~V~~vimentin IF network softens at low ~~s are soft at low stress and~~ strains [37,39,89–91]. Therefore, even if forces from cortical actomyosin are transmitted during cell adhesion to rigid surfaces, the vimentin network averages out these forces, and prevents large curvature deformations that can cause nuclear envelop ruptures. At higher ~~stress and~~ strains, the stiffening of vimentin IFs enables them to dissipate energy and bear the large tensile loads generated by the compression of the environment and increased cytoskeletal contractility. Accordingly, vimentin polymerization increases in response to force application by stiff substrates [42] which may generate a more resilient perinuclear cage. These observations also suggest that the upregulation of vimentin during EMT may protect the nucleus from the high levels of mechanical stress, prevent cell death, and thus promote tumor cell invasion. However, the protection of the nucleus might be a cell-specific function of vimentin. In immune cells, which are specialized to migrate through ~~the~~ confined spaces between endothelial cells, vimentin IFs localize towards the sides of adhesion to endothelial cells and do not appear to form a nuclear cage [92].

Conclusion and perspectives

Despite increasing efforts that show the contribution of IFs in single, collective and 3D migration, the exact mechanisms remain elusive. Current evidence points towards an antagonistic relationship between IFs and actin which is essential for optimal migration. In addition to their unique physical properties, ~~T~~the interaction of IFs with the acto-myosin network, actin-associated adhesions, acto-myosin upstream signaling pathways, (hemi-) desmosomes, and the nucleus provides IFs with the right equipment to steer and tame acto-myosin contractility. It is important to note that the net effects of IFs on cell migration depend on IF composition. Cytoplasmic vimentin and GFAP-containing IFs in astrocytes promote collective cell migration [57] while K6a/b IFs in keratinocytes attenuate migration [60]. Different keratins also play different roles. During epithelial wound healing, migration speed is attenuated as the expression of K6a/b, K16 and K17 increases and that of K1 and K10 decreases. In mesendoderm cells, K8 promotes collective migration [19], whereas in collectively invading breast cancer cells K14 depletion decreases metastasis [93]. Whether these differences result from specific intrinsic properties of the different keratin networks or from IF-type specific interactions with the acto-myosin machinery remains unknown. Dependent on the cell type and mode of migration, IF network composition may be optimized to protect the cell and control the distribution of forces. ~~This may explain the complex role of IFs in migration which either promote or attenuate migration speed.~~ The cell-type specific expression of IFs and the diversity in IF-connections to adhesive structures and to the nucleus coordinate the organization of the IF network in such a way that forces are tempered or allowed where needed. Future studies should focus on these cell-type specific needs of force control by IFs and unravel the mechanisms by which IFs rule over actin during cell migration.

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Figure 1 IF-control over actomyosin optimizes collective cell migration

IFs regulate and interact with the acto-myosin machinery in collectively migrating astrocytes (A) and keratinocytes (B). **A.** Depletion of IFs (GFAP, vimentin and nestin) in collectively migrating astrocytes increases longitudinal stress fibers and decreases interjunctional transverse arcs *(A, right)*. Larger ~~focal adhesion~~FAs and a longer lifetime, discontinuous cell-cell adhesions, and increased ~~-~~traction forces within the migrating monolayer contribute to the loss of collective migration speed and directionality *(A, left)*. These alterations can result from a direct interaction of GFAP and vimentin with the acto-

myosin machinery via the cytoskeletal linker plectin *(box 2)* and/or with ~~focal adhesion~~FA and ~~adherens junction~~AJ components vinculin and talin *(box 1)*. **B.** Depletion of keratin 6a and 6b (K6) decreases ~~focal adhesion~~FA size and lifetime and decreases cell-cell adhesions via desmosomes *(B, left)*. This increases migration speed at the cost of integrity of the re-epithelialized sheet. The interaction between K6 and myosin IIA *(box 3)* is hypothesized to play an important role in the attenuation of collective keratinocyte migration.

Figure 2 The IF-actomyosin interaction via cell-matrix adhesions

A. The interplay between IF-connected hemidesmosomes ~~(HDs)~~ and actomyosin-connected focal adhesions in keratin-expressing epithelial cells. In the presence of hemidesmosomes traction forces exerted at focal adhesions are lower. Near these focal adhesions, keratin IFs align in linear arrays *(box 1)*. Disassembly of hemidesmosomes~~HDs~~, or disconnection of IFs from ~~HDs~~hemidesmosomes, increases focal adhesion size and number, and traction forces. These changes could result from a direct interaction between hemidesmosomes~~HD~~ and FAs *(dotted arrow)*, or result from the interplay between IFs, FAs and acto-myosin *(arrows)*. **B.** The interplay between IF-connected cell-matrix adhesions, FAs, and acto-myosin upstream signaling. In vimentin-expressing epithelial cancer cells, cell-matrix adhesions reminiscent of hemidesmosomes are linked to the IF-network via an α6β4-plectin-vimentin interaction (*box 2*). Vimentin that organizes in linear arrays at these adhesions interacts with, and regulates the dynamics of, β4 integrin and activity of the RhoA-GEF Rac1 that promotes actin polymerization. In the absence of vimentin (B, bottom), Rac1 activity, ~~focal adhesion~~FA numbers, and cell motility are decreased. Vimentin can regulate FAs and actomyosin via ~~Via~~ a direct interaction with for example β1-integrin, via plectin, or via downstream integrin signaling ~~, vimentin can regulate FAs and actomyosin~~ as well *(box 3)*. Arrows indicate how IFs, actomyosin, and cell-matrix adhesions are connected in an integrated system.

Figure 3 The IF nuclear cage protects the nucleus during confined migration.

Confined 3D migration through tight constricted spaces requires actin polymerization at the cell front (protrusive forces), acto-myosin contractility (contractile forces) for rear retraction, and cell squeezing and deformation (compressive forces). Vimentin IFs form a nuclear cage around the nucleus that slows down migration through confined spaces (top). Vimentin depletion increases confined migration (bottom) but induces DNA damage, nuclear blebbing and cell death. Vimentin IFs form a nuclear cage that protects the nucleus from forces induced by the environment and by ~~–~~strong acto-myosin contractility during confined 3D migration.

Figure

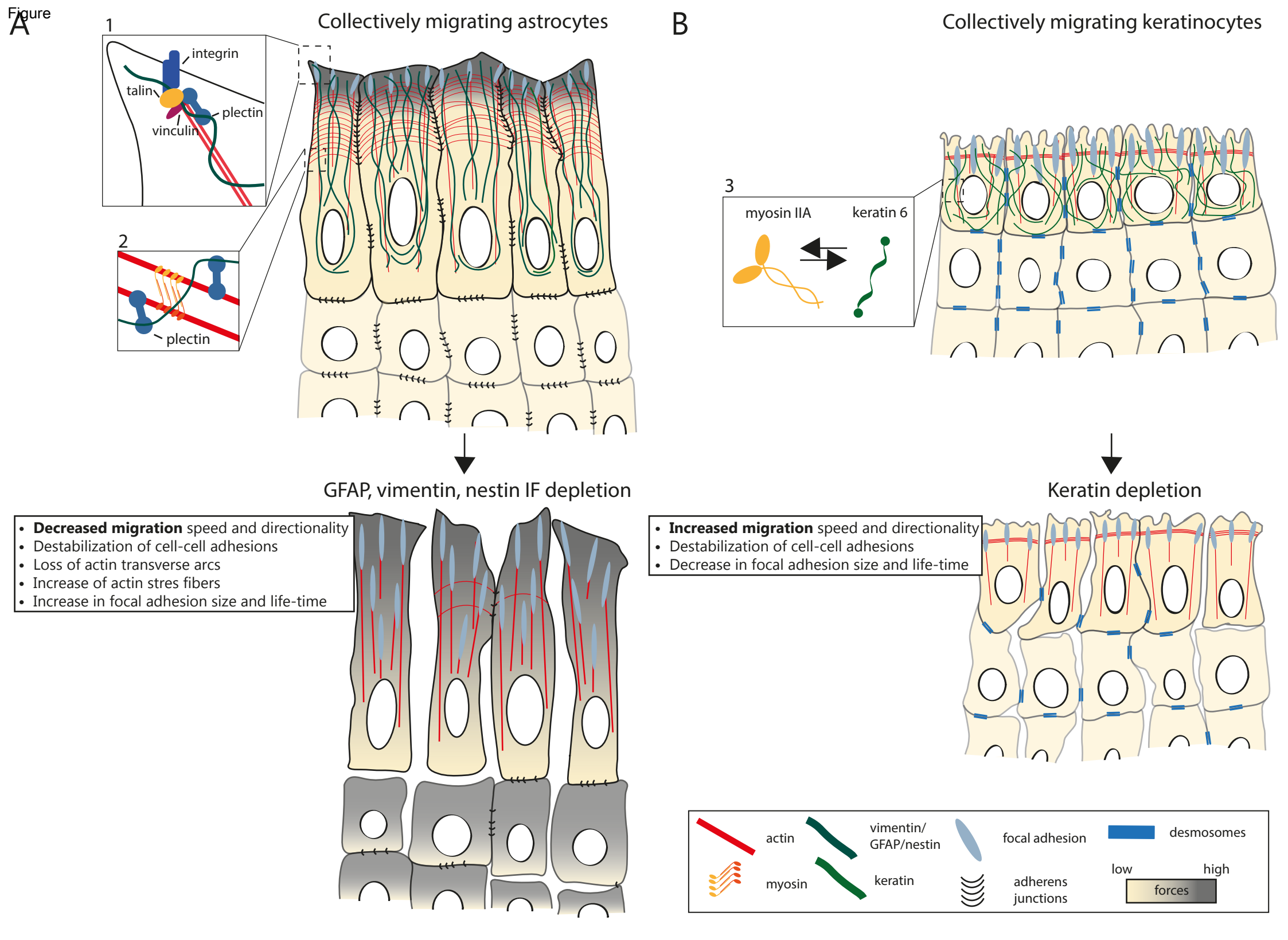

A
1
integrin
talin
plectin
vinculin
2
plectin
Collectively migrating astrocytes
GFAP, vimentin, nestin IF depletion
• **Decreased migration** speed and directionality
• Destabilization of cell-cell adhesions
• Loss of actin transverse arcs
• Increase of actin stres fibers
• Increase in focal adhesion size and life-time
B
Collectively migrating keratinocytes
3
myosin IIA
keratin 6
Keratin depletion
• **Increased migration** speed and directionality
• Destabilization of cell-cell adhesions
• Decrease in focal adhesion size and life-time
actin
myosin
vimentin/
GFAP/nestin
keratin
focal adhesion
adherens
junctions
desmosomes
low
high
forces

Figure 2

A

Keratin-expressing epithelial cell

actomyosin

IF

HD

FA

1

Hemidesmosome

keratin linear arrays

α6β4

plectin

laminin

ECM

HD disassembly

- Increased contractility
- Increased focal adhesion number and size
- Increased traction forces

B

Vimentin-expressing mesenchymal/cancer cell

actomyosin

IF

HD-like adhesion

FA

2

Rac1

vimentin

Vimentin depletion

- Decreased cell motility
- Decreased focal adhesion number
- Decreased Rac1 activity

3

integrin

signaling molecules

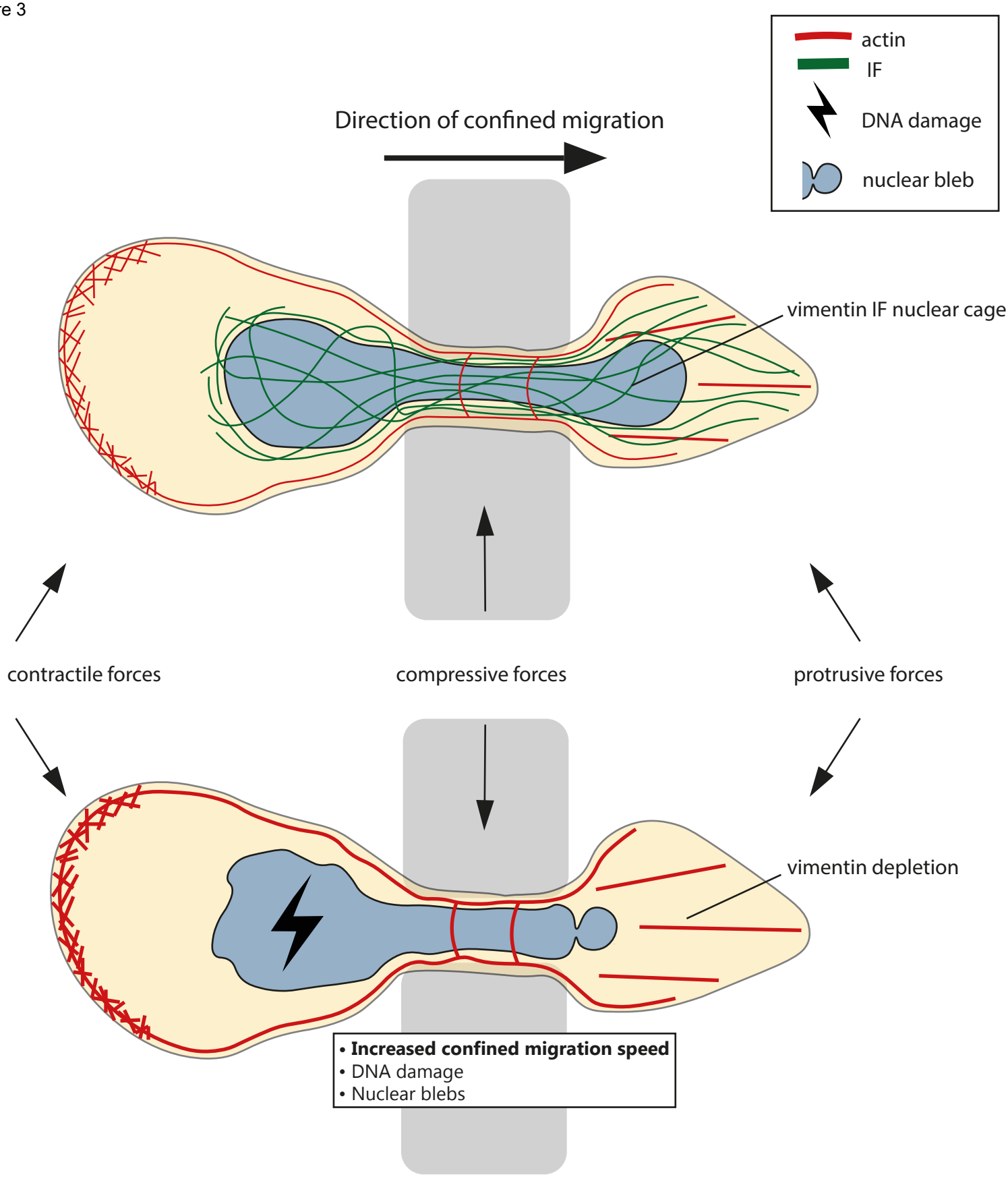
1 2 3

plectin

1. direct IF-integrin interaction
2. IF-integrin interaction via plectin
3. IF interaction with downstream integrin signaling molecules

actin myosin keratin vimentin plectin hemidesmosome focal adhesion integrin α6β4

Figure 3


actin
IF
DNA damage
nuclear bleb
Direction of confined migration
vimentin IF nuclear cage
contractile forces
compressive forces
protrusive forces
vimentin depletion
• Increased confined migration speed
• DNA damage
• Nuclear blebs

INSTITUT PASTEUR

Paris, le 15/02/20

Cell Polarity, Migration and Cancer Unit

Institut Pasteur

25 rue du Dr Roux, 75724 Paris cedex 15

FRANCE

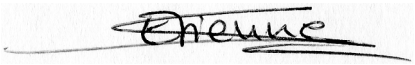
De : *Etienne-Manneville Sandrine*

Telephone : *01 40 61 39 05*
FAX : *01 45 68 85 48*
E-mail : *setienne@pasteur.fr*

OBJET : Conflict of Interest

I and the authors declare no conflict of interest

Sandrine Etienne-Manneville, Emma van Bodegraven



Sandrine Etienne-Manneville, PhD