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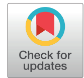
Dealing with the nucleus during cell migration



Francisco J Calero-Cuenca, Cátia S Janota and Edgar R Gomes

The position of the nucleus within cells is a key event during cell migration. The movement and positioning of the nucleus strongly impacts cell migration. Notably, the last two years largely contributed to emphasise the dynamicity of the nucleus–cytoskeleton interactions that occur during cell migration. Nuclei are under continuous tension from opposing intracellular forces and its tether to the cytoskeleton can be regulated at different levels. Interestingly, it was showed how nuclear positioning is highly related to cell function. In most migrating cells, including cancer cells, the nucleus can be the rate limiting step of cell migration and is placed away from the leading edge. By contrast, leukocytes position their nucleus close to the lamellipodia at the leading edge, and the nucleus contributes to drilling through the endothelium. Differences in cell migration in 2D versus 3D environments are also evident. The mechanisms and forces at play during nuclear positioning and translocation are clearly affected by the nature of the substrate. As such nuclear positioning during cell migration can vary between cell types and environments. In this review we aim to give an overview of the latest discoveries in the field revealing how nuclear positioning is tightly regulated, not only by intrinsic nuclear properties, such as deformability, nuclear envelope content or nucleus–cytoskeleton connectivity, but also by the microenvironment.

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Introduction

In eukaryotic cells, the nucleus is actively positioned at a specific place within the cytoplasm according to different biological processes, such as cell division, differentiation or migration [1,2]. Differentiated cells, such as neurons, myofibers, epithelial cells or immune cells exhibit a precise nuclear position and architecture that strongly impacts their functions. Deregulation of these nuclear characteristics is usually associated with cell dysfunction and disease [1,3]. In recent years, nuclear positioning and structure were shown to be crucial for cell migration. Even though cell migration is essential for tissue development and homeostasis, it can also play a detrimental role during cancer metastasis and inflammation. Our current understanding of cell migration comes mostly from studies in two dimensions (2D) in which cells move on a flat substrate. These studies uncovered the importance of focal adhesions, the cytoskeleton and their connection to the nucleus for proper cell migration. However, when three dimensions (3D) substrates are used cells must migrate under multiple confinements, thus leading to the identification of novel mechanisms regulating cell migration [4,5]. Cell migration and invasion in an *in vivo* context require cells to pass through different barriers such as the extra-cellular matrix (ECM) or neighbouring cells. Cells must pass through pores sometimes with sizes much smaller than the cell itself. While cytoplasm, plasma membrane and most of the small organelles are easily adjustable to pass through these pores, the nucleus is the main restricting component due to its size and stiffness [6,7]. To overcome these obstacles, cells use two main mechanisms: (a) modulate the ECM matrix in order to increase the size of the pores and/or (b) regulate nuclear dynamics in order to deform its shape and reduce nuclear stiffness and rigidity. In this review we discuss the most recent insights regarding the mechanisms that regulate nuclear positioning, translocation, shape and rigidity during cell migration. In particular, we analyse the differences between cell migration on 2D and 3D substrates, as well as differences among cell types, pointing out the future challenges of the field.

Positioning the nucleus before migration

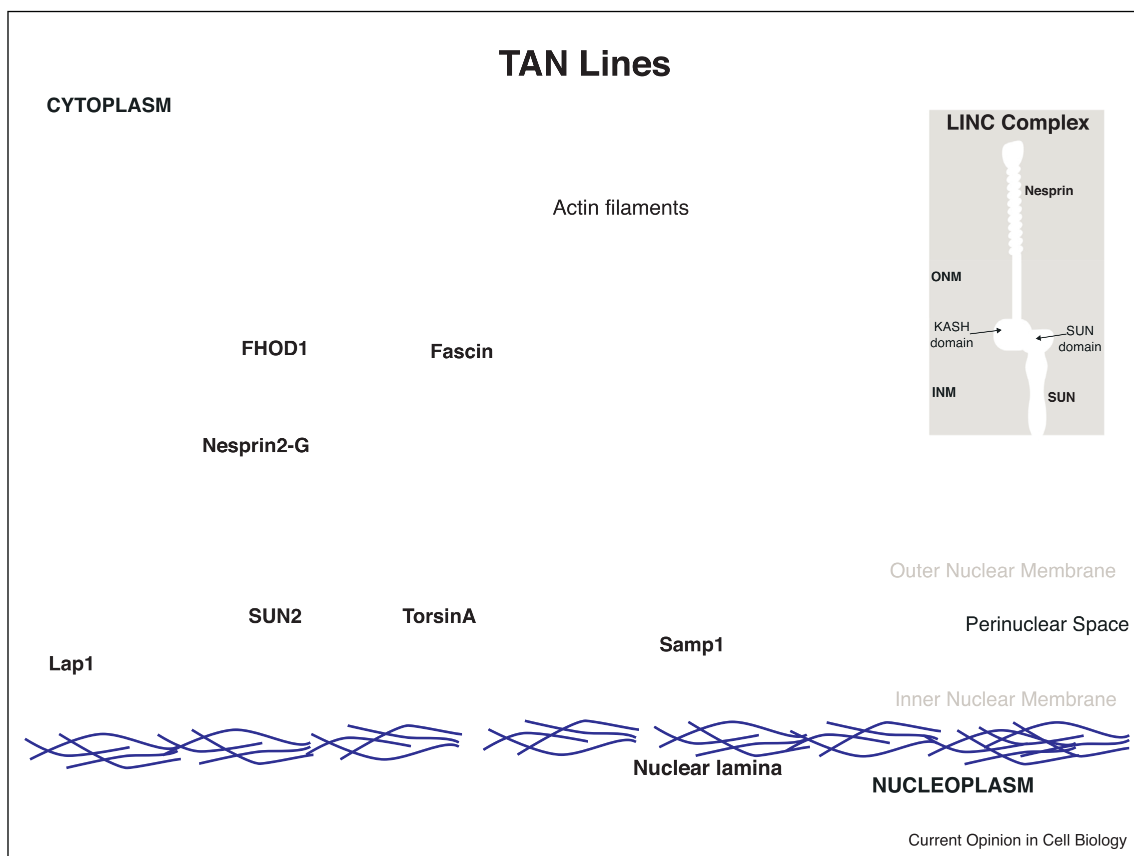
The architecture of cells changes in preparation for migration. Organelles and cytoskeleton are re-arranged providing polarity to the cell in the direction of migration. During this process, the position of the nucleus becomes particularly relevant. In polarized fibroblasts, neurons, mesenchymal cells and most cancer cells, the nucleus is positioned to the cell rear creating a leading edge/centrosome/nucleus axis in the direction of migration [8–11]. This rearward nuclear movement, initially described in migrating fibroblasts, is driven by an actin retrograde flow mediated by myosin and Cdc42 [9]. Actin retrograde flow is coupled to the nuclear envelope (NE) by the LINC complex, the main tether between the nucleus and the cytoskeleton, composed of NE nesprin and SUN proteins [12,13]. Nesprin-2 and SUN2, together with actin filaments, form TAN (Transmembrane Actin-associated Nuclear) lines that tether the nucleus to the actin

cytoskeleton thus allowing the movement of the nucleus by the actin retrograde flow [14].

Several proteins that regulate the formation and dynamics of the TAN lines were recently identified (Figure 1). Samp1 anchors the LINC complex to the nuclear lamina through SUN2 stabilizing the LINC complex at the TAN lines [15]. The nuclear envelope-localized AAA+ TorsinA and its activator LAP1, regulate actin retrograde flow of dorsal perinuclear actin and the assembly of the TAN lines [16]. Additionally, the formin FHOD1 and the protein Fascin, both actin dynamics regulators, interact with Nesprin-2 thereby providing two additional connections for the LINC complex with actin cables. Whereas the role of FHOD1 in nuclear movement was described in 2D migration and may provide a new level of regulation through GTPases [17], the role of Fascin seems to be more relevant during 3D migration since Fascin KD cancer cells are unable to deform the nucleus during migration through confined spaces [18].

These studies support that NE-actin tethering is sustained by the direct interaction of actin with Nesprin-2 as well as additional interaction sites mediated by other proteins. These multiples connections allow diverse levels of regulation that could come into play for different cellular processes. It would be important to know if there are other NE-actin connections regulating nuclear movement, if they are LINC-independent, how all these connections are regulated and in which manner this regulation affects cell migration. This can be especially relevant since the involvement of the LINC complex and TAN lines were discovered in 2D cell migrating studies. As such the extent to which these known players

Figure 1



TAN lines connect the nucleus to the actin cytoskeleton for nuclear positioning during migration. The LINC complex is the main link connecting the nucleus to the cytoskeleton and it is composed by SUN proteins located in the inner nuclear membrane and Nesprins proteins at the outer nuclear membrane. The interaction occurs in the perinuclear space between the SUN and KASH domains. Regarding rearward nuclear movement in 2D migration, SUN2 interacts with Nesprin-2G which binds to the actin filaments on the top of the nucleus forming TAN lines. In this way, the actin retrograde flow is connected to the nucleus in order to position the nucleus properly. Since the discovery of the TAN lines, many proteins have been identified as regulators of the LINC complex in this process, which was shown to affect its localization and its interaction with actin. Fascin and FHOD1 provide new links between Nesprin-2G and actin, increasing the level of regulation. Samp1 and Lamin A/C stabilize the LINC complex at the nuclear envelope. TorsinA and LAP1 are necessary for TAN lines assembly and persistence, as well as retrograde flow of dorsal perinuclear actin.

participate in 3D migration and in *in vivo* remains an open question.

Even though rearward nuclear movement in migrating cells is a well-described mechanism, the existence of a 'brake' that could act in the same process to control the proper position of the nucleus is still unknown. In a recent work, centrifugal forces were applied to fibroblast monolayers with wounds in order to produce a nuclear displacement towards the front or the back of the cell depending on the relative position to the wound [19•]. This assay elucidated two different mechanisms of nuclear re-centering: (a) an actomyosin, Nesprin-2G and SUN2 dependent rearward nuclear re-centering and (b) a microtubule, dynein, Nesprin-2G and SUN1 dependent nuclear re-centering towards the front of the cell. This work, directly demonstrates that the nucleus is subjected to continuous and opposite forces and its position results from the dynamic control of the LINC complex and cytoskeleton [20]. In fact, such forces were recently demonstrated to be directly applied to the LINC complex and showed to have a mechano-sensing role by sensing tension from cell-cell junctions and focal adhesion at the NE [21,22]. The unbalance of any of these mechanisms of nuclear recentering would favour the movement of the nucleus specifically in one direction. How these mechanisms could affect cell function and cell migration is something that needs to be addressed.

Moving the nucleus during migration

During 2D migration the nucleus translocates together with the cell body in a myosin II dependent manner, that both pushes and pulls the nucleus [23,24]. This role for actomyosin was also described in 3D substrates [25–28]. Alongside actomyosin-mediated movement, recent works showed a role for perinuclear actin network in protecting the nucleus and facilitating nuclear translocation during cell migration. Skau *et al.* showed that the formin FMN2 is essential to generate a perinuclear actin/focal adhesion system that controls nuclear positioning in 2D, protects from DNA damage and promotes cell migration under confinement (in MEFs) as well as *in vivo* (in melanoma cells) [29••]. Alternatively, Thiam *et al.* demonstrated that the Arp2/3 complex nucleates actin around the nucleus in dendritic cells. This actin nucleation promotes Lamin A/C perturbation in the nuclear lamina facilitating nuclear deformability and increasing the ability to migrate through narrow constrictions [30].

The role of other cytoskeleton components such as microtubules in nuclear positioning during migration remains to be elucidated. Although in 2D migration microtubule dynamics seem to be dispensable for rearward nuclear movement [9], they are necessary for nuclear movement in other contexts such as nuclear migration in neurons, skeletal muscle development or hypodermal cells in *C. elegans* [31–33]. Moreover, dynein is involved in nuclear rotation and centrality in migrating fibroblasts [34].

Regulating intrinsic nuclear properties to move the nucleus

The size and stiffness of the nucleus constitutes a limitation for 3D cell migration. Live imaging of migrating cells through tight spaces has shown that nuclei are drastically pushed, pulled and deformed in order to progress [6,7]. Two main players determine the rigidity and viscosity of the nucleus: chromatin and nuclear lamina.

Chromatin occupies most of the nuclear space and is organized as euchromatin, de-condensed DNA that is actively transcribed, or as heterochromatin, condensed DNA usually associated with silenced genes. Each configuration confers different viscosity to the nucleus. Consequently, the ratio between euchromatin and heterochromatin can modulate nuclear stiffness and affect cell migration [35,36]. However, this hypothesis is still under debate and thus needs to be further investigated. A recent study has opened new possibilities in this debate. It was observed that cells have the capacity to regulate their water content in response to different microenvironments, ultimately leading to changes in molecular crowding, including DNA in the nucleus [37]. This work raises further questions such as if nuclear stiffness can change upon water influx or if cells can regulate their water content before squeezing. Furthermore, the mechanisms regulating water efflux would need to be identified. This work is reminiscent of a previous finding in lamellipodia-independent 3D cell migration where actomyosin network pulls the nucleus forward increasing the cytoplasmic hydraulic pressure in the front of the cell facilitating lobopodial membrane formation [26]. Thus the nucleus acts as a piston to increase the hydraulic pressure in the front of the cell. It would be interesting to test if cells are regulating cell volume on the anterior part of the cell when they switch to piston-driven migration.

The main components of the nuclear lamina are the type V intermediate filaments lamins, Lamin A/C and Lamin B, which form a cytoskeleton network beneath the nuclear envelope. Lamin A/C connects the nucleus to the cytoskeleton via the LINC complex since they bind to the SUN proteins. Lamin A/C is also a key element regulating nuclear shape and rigidity [38]. Downregulation of lamin A/C expression is found in cells with high migratory capacity and is associated to metastasis [39,40].

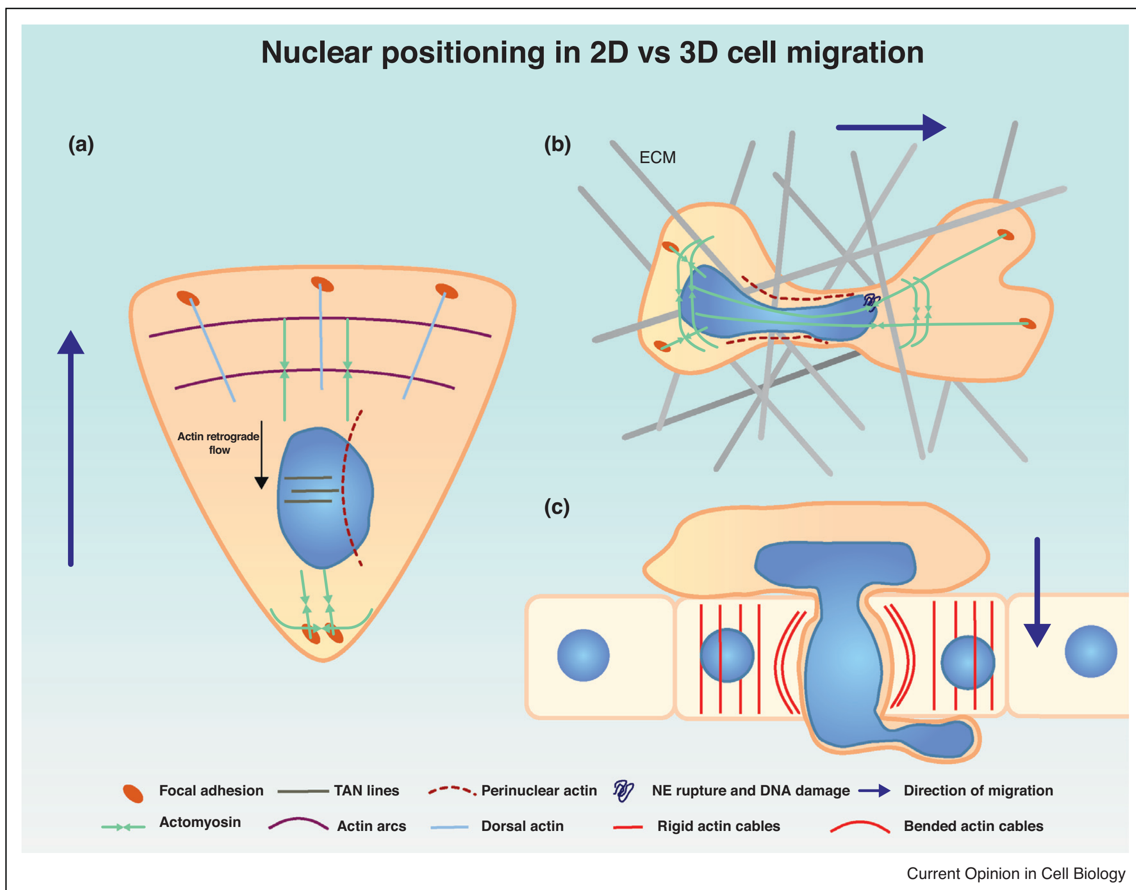
Recent work showed a new mechanism by which cells migrate in confinement based on NE rupture and repair. During migration through tight spaces, nuclei of immune and cancer cells experience a peak in intracellular pressure and deformation that results in NE breakdown. This usually occurs in regions with high NE curvature and reduced nuclear lamina. The NE rupture produces DNA

damage and uncontrolled cytoplasm–nucleus trafficking that affects genome stability. Cells use the ESCRT III machinery to promptly reseal the breaks and repair the DNA in order to minimize injury [41•,42•]. This mechanism could be used to reduce nuclear resistance during cell migration in other conditions. However, NE rupture is not always observed upon nuclear squeezing. During muscle fibres development, myonuclei squeeze to the periphery of myofibers without NE breakage [43]. Instead, softening of the nucleus is probably modulated by local alterations in Lamin A/C distribution as was previously observed in other cell types [39,44]. The existence of another mechanism that protects the NE integrity in this process is still unknown. It would be interesting to identify the threshold for NE rupture and how cells regulate this resistance during cell cycle. Moreover, further investigations are needed to determine how NE rupture and repair can be targeted against cancer metastasis, how it affects genome transcription and cell function, as well as whether it is used in other biological contexts.

When the nucleus leads the way during migration

It was recently observed that cells position their nucleus at the forefront of the cell during migration. Alon's group investigated the trans-endothelial migration (TEM) of leukocytes and more specifically how immune cells are able to generate gaps and squeeze in between endothelial layers. Under shear flow, the TEM is independent of endothelial actomyosin contractility in different types of leukocytes *in vitro* as well as endothelial Rho kinase

Figure 2



Nuclear positioning is uniquely regulated during cell migration, depending on the substrate and cell type. During 2D migration **(a)**, the nucleus is positioned away from the leading edge by actin retrograde flow that connects to the nuclear envelope by the LINC complex. The proteins Nesprin-2 and SUN2 form linear arrays in the nuclear envelope that connect to actin filaments, forming the TAN lines. Posteriorly, the actomyosin and focal adhesion network is essential to translocate the nucleus. In 3D substrates, many cells position their nuclei away from the leading edge and the nucleus is the rate limiting step for cells to penetrate through tiny spaces, as occurs during metastasis **(b)**. Cells need to push and pull the nucleus that has to be highly deformed. In this way, the stiffness and rigidity of the nucleus acquires a great relevance. In some situations, nuclear envelope rupture occurs and that results in DNA damage. Cells present different mechanisms to solve this problem, as activation of the ESCRT-III machinery or formation of a perinuclear actin network that protects the nucleus. Interestingly, some cell types such as leukocytes, position their nucleus in the leading edge in order to bend the actin filaments of endothelial cells during transendothelial migration **(c)**.

Table 1

Nuclear positioning in 2D and 3D cell migration.

2D migration	3D migration
Nucleus positioned usually to the back	Nucleus positioned in the back or front depending on the cell type
Actin retrograde flow positions the nucleus	High dependence on actomyosin contractility
TAN lines dependent	High nuclear deformability
Low nuclear deformability	High dependence on nuclear stiffness and rigidity mediated by lamin A/C and DNA condensation
Lamin A/C stabilizes the LINC complex at the nucleus	Nuclear envelope rupture and DNA damage

activity in neutrophils *in vivo* [45••]. This work reveals that nuclei from uni-lobular T cells can transpose endothelial barriers as fast as the three-lobular neutrophils despite significant disparity in lamin A/C expression [46]. Moreover, the authors show that T cells must incorporate small nuclear lobes in their lamellipodia using myosin-II in order to transmigrate, whereas in the endothelial cells myosin-II is not necessary for the TEM. Once a leader lobe slides into a lamellipodia, a transcellular pore or a paracellular gap is formed, allowing transmigration of these immune cells. Thus, these studies suggest that the nucleus can be important to drill through endothelial monolayers. The mechanism behind this process and how it is regulated is currently unknown and it would be of great value to clarify the mechanism behind the fast nuclear displacement that precedes the drilling phase.

Concluding remarks

The nucleus is the largest organelle in eukaryotic cells and its dynamics has an important role in different cell functions such as cell migration. In the last few years, studies have underlined the importance of accurately positioning nuclei within cell for cell migration. The first studies were performed on 2D substrates and allowed the identification of connections between the cytoskeleton and the NE and the mechanisms underlying nuclear positioning and translocation during cell migration. More recently, the use of 3D substrates revealed other mechanisms for nuclear positioning. In most cases, the nucleus is the principal obstacle for cells to migrate through tight spaces, such as during metastasis. In those cases, the nucleus remains at the rear of the cell, is pulled, pushed and undergoes deformations and disruptions to go through small constrictions. However, some cells position their nuclei at the leading edge and use it as a tool to drill holes through obstacles like an endothelial layer in order to migrate (Figure 2 and Table 1). The diverse strategies adopted by cells to position their nucleus in order to migrate prompts many subsequent biological questions all while reinforcing the importance of nuclear positioning and dynamics during cell migration. Why does the nucleus has so different behaviour depending on the cell type and process? What are the mechanisms regulating the asymmetrical position of the nucleus during migration? How do the intrinsic properties compete and sense the microenvironment stimuli? Understanding how the different cytoskeleton components are regulated between them and how they are connected to the NE and the nucleoskeleton will help addressing these questions. Additionally, efforts should also be focused on 3D and *in vivo* models to identify possible targets implicated in human disorders. Finally, a recent work showed how microenvironmental forces applied to the nucleus clearly affect nuclear pore properties and regulate nucleus–cytoplasm trafficking of YAP [47•]. Further investigations about how nuclear squeezing regulate gene expression will open a new level of complexity and it will be important to better define the role of nuclear dynamics during cell migration.

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