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Dealing with the nucleus during cell migration

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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

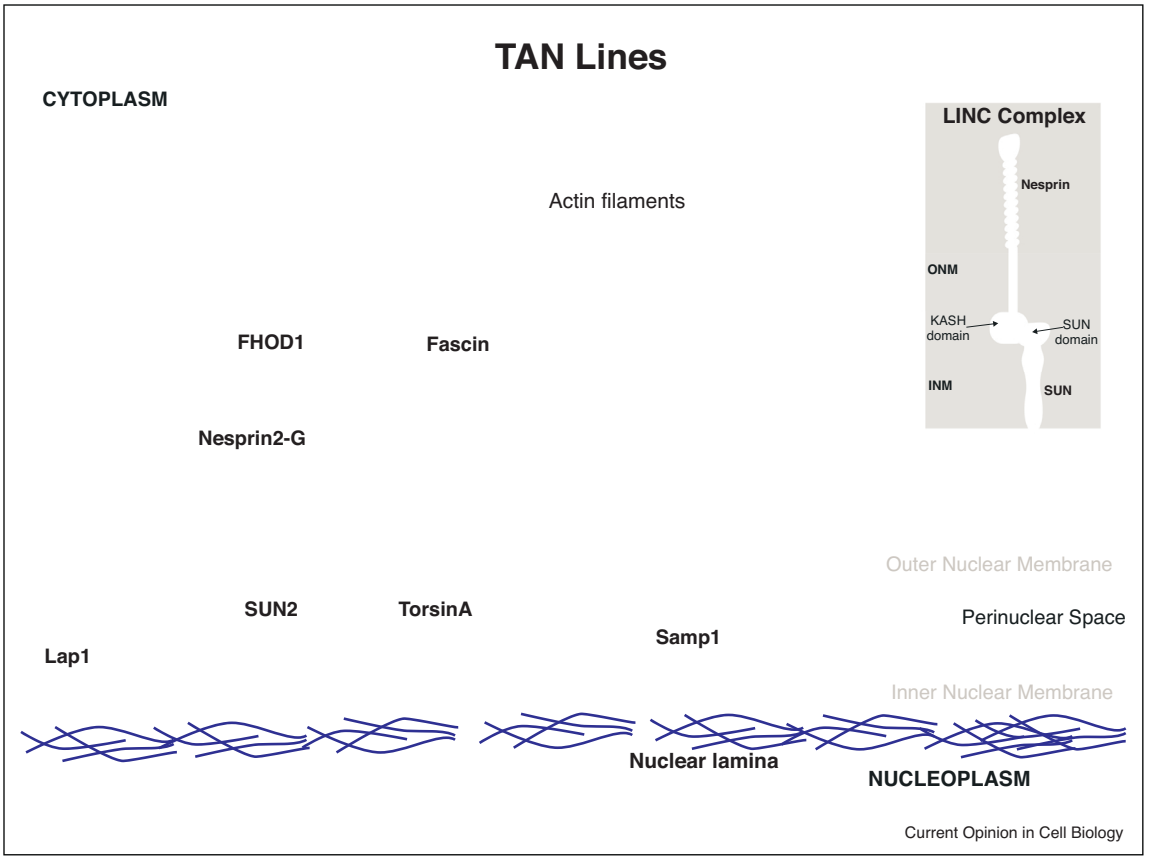
The architecture of cells changes in preparation for migration. Organelles and cytoskeleton are re-arranged providing polarity to the cell in the direction of migration. During this process, the position of the nucleus becomes particularly relevant. In polarized fibroblasts, neurons, mesenchymal cells 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.