Experimental Cell Research 348 (2016) 56–65

Contents lists available at ScienceDirect

Experimental Cell Research

journal homepage: www.elsevier.com/locate/yexcr

Review article

Nucleus and nucleus-cytoskeleton connections in 3D cell migration

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ARTICLE INFO

Article history:
Received 15 May 2016
Received in revised form
2 September 2016
Accepted 3 September 2016
Available online 5 September 2016

Keywords:
Nuclear mechanics
Migration
Chromatin
Lamins
LINC complex
Cytoskeleton

ABSTRACT

Cell migration plays an important role in many physiological and pathological settings, ranging from embryonic development to cancer metastasis. Currently, accumulating data suggest that cells migrating in three-dimensional (3D) environments show well-defined differences compared to their well-established two-dimensional (2D) counterparts. During 3D migration, the cell body and nucleus must deform to allow cellular passage through the available spaces, and the deformability of the relatively rigid nucleus may constitute a limiting step. Here, we highlight the key evidence regarding the role of the nuclear mechanics in 3D migration, including the molecular components that govern the stiffness of the nucleus and review how the nuclear dynamics are connected to and controlled by cytoskeleton-based migration machinery. Intriguingly, nuclear movement must be coordinated with the cytoskeletal dynamics at the leading and trailing edges, which in turn impact the cytoplasmic dynamics that affect the migration efficiency. Thus, we suggest that alterations in the nuclear structure may facilitate cellular reorganizations that are necessary for efficient migration.

Contents

Abbreviations: 2D, Two dimension; 3D, Three dimension; ECM, Extracellular matrix; GCL, Germ cell-less; HDAC, Histone deacetylase; HMT, Histone methyltransferases; HP1, Heterochromatin protein 1; INM, Inner nuclear membrane; LAP2β, Lamina-associated polypeptide-2β; LBR, Lamin B receptor; LINC, Linker of nucleoskeleton and cytoskeleton; NE, Nuclear envelope; Nesprins, Nuclear envelope spectrin repeat proteins; NPCs, Nuclear pore complexes; ONM, Outer nuclear membrane; SUN, Sad1p, UNC-84; TAN, Transmembrane actin-associated nuclear; TSA, Trichostatin A

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http://dx.doi.org/10.1016/j.yexcr.2016.09.001
0014-4827/

1. Introduction

Cell migration is a fundamental phenomenon that is essential for embryonic development and throughout life. It is important for numerous physiological processes and pathological processes including wound healing, immune cell trafficking and tumor metastasis [1,2]. There is considerable interest in understanding the fundamental mechanisms of cell migration because this understanding could lead to medical advances such as retarding the invasion of white cells in the inflammatory process, enhancing the healing of wounds, or abating the spread of highly malignant cancer cells. Cell migration is a complex physicochemical process that requires motor proteins and coordinated structural changes in many cellular components [3]. However, most cell migration studies have focused on the signaling molecules and the dynamics of the cytoskeleton, whereas little is known about the role of the nucleus and its connection to the cytoskeleton, which may play important roles in cell migration.

The migrating cell is viewed as a polarized entity with rapidly changing activities, particularly at the leading edge and trailing end [3]. Some researches on migration modes are dedicated exclusively to two-dimension (2D) environments [4], such as those used by epithelial keratocytes and keratinocytes [5]. Many cells grown on 2D substrates display a characteristic cellular polarization before initiating migration [6,7]. Nucleo-cytoskeletal coupling is required to dynamically position the nucleus on the basis that depletion of lamins or disruption of the LINC (linker of nucleoskeleton and cytoskeleton) complex prevents rearward nuclear movement [8–10]. In addition, the stiffness of the nucleus could affect the forces applied to it by the cytoskeleton. Forces applied to a stiffer nucleus would remain more focused, making it easier to regulate its shape and the direction of migration [11].

However, cell motility in vivo usually takes place in three-dimension (3D) environments. It is now becoming evident that cell migration in 3D interstitial tissues differs substantially from cell migration on 2D substrates [6]. During migration through 3D interstitial tissues, the stiffness of the surrounding extracellular matrix (ECM) present a challenge to the moving cell body. Cells have two principal mechanisms to move through confining space: (i) widening the gap through proteolytic ECM degradation [12] and (ii) changing their shape and stiffness to fit the available space [13]. For a cell passing through a constriction that is smaller than the cell diameter, the shape of the cell body thus adapts its morphology and thereby minimizes the resistance of the restrictive tissue [14]. In the context of these large modifications of the morphology, nucleus, the largest eukaryotic organelle, is stiffer than the surrounding cytoskeleton. The structure and composition of the nucleus play a critical role in nuclear mechanics by determining the nuclear shape and stiffness. Recently, it has been reported that the nuclear protein composition is altered during cell migration [15]. In contrast to the observations for 2D migration, a negative correlation between the expression of lamin A/C and migration efficacy was observed, which was consistent with the principle that decreased nuclear stiffness is associated with increased 3D migration [16–18]. One potential mechanism by which changes in the nuclear protein composition could contribute to cell migration is that softer nuclei could facilitate cell passage through 3D tissues [19,20]. These discrepancies may be a consequence of the different dimensionalities of the migration substrates and the fact that compensation for the lamin A/C modulation-induced changes in mechanocoupling cannot be achieved on a 2D surface. Furthermore, the mechanical coupling between the nucleus and the cytoskeleton is critical for cell polarization, which could affect cell migration [21]. In this review, we aimed to integrate the nuclear dynamics into the multistep model of cell migration, and we discuss the implications of nuclear mechanics for cell migration.

2. Nuclear dynamics during cell migration

2.1. Nuclear translocation for migration

The steps of the migration cycle involve dynamic interactions between the nucleus and the cytoskeleton [22]. During this process, the movement of the nucleus must be coordinated with the cytoskeletal dynamics at the leading and trailing edges [23]. Upon initiation of migration, cytoskeletal cell elongation is followed by rotation of the nucleus [24]. Subsequently, the nucleus first moves towards the leading edge or trailing edge [25]. The nuclear relocation predominantly depends on the actomyosin network-mediated contraction of the actin filaments and shortening of the cell tail, which results in the nucleus being pushed forward. Inhibition of myosin II leads to defects in nuclear relocation and tail retraction [26]. Therefore, cell migration is associated with the cytoskeleton-mediated translocation of the nucleus within the migrating cell.

2.2. The size and stiffness of the nucleus pose a physical obstacle for cell migration

During 3D cell migration, the shapes of both the cytoplasm and nucleus have to be adjusted to facilitate passage of the migrating cell through confining environments. The combination of the large size and relative stiffness of the nucleus led to the hypothesis that the ability of the cell to compress the nucleus can become a rate-limiting factor in penetrating small pores [20]. During this process, the nucleus undergoes a remarkable deformation, which leads to a local compression of the cell that generates large forces that are transmitted through the cytoskeleton to the nucleus. These forces in turn cause nuclear deformation into an irregular shape (Fig. 1), as observed in leukocytes [27], neurons [28] and some cancer cells [14]. In some highly mobile cell types, including myeloid and metastatic cells, the nuclei are bean-shaped or segmented instead of the classical spherical shape and thus may develop greater morphological flexibility [3]. Thus, both location and extent of deformation of the nucleus during cell migration depend on the diameter of the nucleus.

In addition to the size of the nucleus, its relative stiffness can also pose a major obstacle for cellular migration (Fig. 2A). Various experimental techniques have been developed to probe the stiffness of the nucleus [29–35]. Recent experiments have shown that the nucleus exhibits both elastic and viscoelastic properties and is approximately 2- to 10-times stiffer than the cytoplasm [36]. The nuclear stiffness results from a multiple determinants that include the level of chromatin compaction as well as the lamin A/C content