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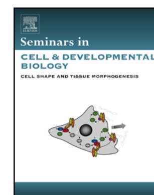

Review

Nuclear positioning in migrating fibroblasts

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ABSTRACT

The positioning and movement of the nucleus has recently emerged as an important aspect of cell migration. Understanding of nuclear positioning and movement has reached an apogee in studies of fibroblast migration. Specific nuclear positioning and movements have been described in the polarization of fibroblast for cell migration and in active migration in 2D and 3D environments. Here, we review recent studies that have uncovered novel molecular mechanisms that contribute to these events in fibroblasts. Many of these involve a connection between the nucleus and the cytoskeleton through the LINC complex composed of outer nuclear membrane nesprins and inner nuclear membrane SUN proteins. We consider evidence that appropriate nuclear positioning contributes to efficient fibroblast polarization and migration and the possible mechanism through which the nucleus affects cell migration.

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1. Introduction

Mesenchymal-derived fibroblasts are the most common cells in many connective tissues where they produce the extracellular matrix and other factors that are important for tissue and organ homeostasis and repair. Their role in these processes critically depends on their ability to migrate. Poor migration leads to wound healing defects, for example in aged individuals [1,2], whereas uncontrolled migration contributes to inflammation and scarring [3]. Beyond their physiological importance, fibroblasts have provided an important test bed for exploring basic mechanisms of migration due to their robustness in culture and as well as their inherent propensity to migrate.

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The nucleus has emerged as a surprisingly important factor in the migration of fibroblasts and other cell types. Depending on the environment, the nucleus contributes to migration by providing polarity, integrating intracellular forces, generating intracellular pressure for propulsive force, and impeding movement through narrow constrictions. How the nucleus is moved and positioned for these activities has received much attention over the last 10 years. These studies have revealed that distinct linker of nucleoskeleton and cytoskeleton (LINC) complexes contribute to nuclear movement and positioning in fibroblasts. LINC complexes are composed of outer nuclear membrane KASH proteins (or nesprins/Synes in vertebrates) and inner nuclear membrane SUN proteins that interact within the perinuclear space [4,5]. Depending on the nesprin employed and the environment, the nucleus can attach to actin filaments, microtubules (MTs) or intermediate filaments (IFs) [6–8].

Advances have been made in understanding the role of LINC complexes in both 2D and 3D fibroblast migration. On one hand, nuclear movement has been extensively studied in 2D fibroblasts polarizing for migration in wounded monolayers. This has been a powerful system to identify the molecular components connecting the nucleus and cytoskeleton due to the ease of both genetic and cell biological manipulations and the high resolution imaging possible with flat, well-spread cells. Indeed, a macromolecular assembly of specific LINC complexes, actin cables and associated proteins has been observed to assemble during active nuclear translocation accompanying fibroblast polarization for migration [9–11]. Moreover, distinct adhesion-like structures beneath the nucleus have been described and reported to cause defects in nuclear positioning [12]. On the other hand, a novel mechanism dependent on nesprin-3, termed the “nuclear piston”, has been identified and contributes to lobopodial migration of fibroblasts migrating in 3D environments [13].

Here we review recent studies examining nuclear positioning and movements in fibroblasts polarizing for migration and during active fibroblast migration in 2D and 3D environments. In each case, we consider the molecular and mechanical mechanisms for these events, the pathways regulating them, and the roles played by nuclear positioning in fibroblast polarization and migration.

2. Nuclear translocation in fibroblasts polarizing for migration in 2D

In many migrating cells, including fibroblasts, the nucleus is positioned rearward of the cell centroid [8]. Fibroblasts have an intrinsic mechanism to establish this rearward position of the nucleus, independent of actual cell migration, as shown by experiments with serum-starved wounded monolayers [14]. Addition of the serum factor lysophosphatidic acid (LPA) to wounded monolayers of starved NIH3T3 fibroblasts or mouse embryo fibroblasts (MEFs) triggers rearward translocation of the nucleus without stimulating migration (Fig. 1A). This nuclear translocation is not accompanied by nuclear rotation or changes in nuclear shape making its analysis less complex than nuclear positioning and movements that occur in actively migrating fibroblasts. As the centrosome is maintained at the cell centroid during rearward nuclear translocation, movement of the nucleus creates cell polarity by orienting the centrosome toward the leading edge (Fig. 1A). Intriguingly, live cell recordings of starved NIH3T3 fibroblasts stimulated to migrate by serum reveal that productive migration commences when the nucleus moves rearward and the centrosome is oriented [14]. This result suggests that proper rearward positioning of the nucleus and centrosome orientation are required for productive fibroblast migration, a conclusion consistent with the inhibition of migration when the pathways regulating rearward translocation are disrupted (see below).

2.1. LINC complexes assemble into higher ordered TAN lines to translocate the nucleus

The rearward nuclear translocation in fibroblasts stimulated by LPA is inhibited by actin and myosin drugs and occurs at the same velocity as actin retrograde flow, indicating an actomyosin process [14]. Numerous results indicate that actin directly connects to the nucleus to move it. Dominant negative and knockdown approaches show that nesprin-2 giant (nesprin-2G) is required for nuclear movement [10,15,16]. Nesprin-2G is one of two giant nesprins (nesprin-1G is the other) that contain actin-binding, calponin homology (CH) domains and is the only one expressed in NIH3T3 fibroblasts [10]. Impaired nuclear movement in NIH3T3 fibroblasts depleted of nesprin-2G is rescued by expression of mini-nesprin-2G (mini-N2G), a chimeric construct containing the N-terminal CH domains and the C-terminal KASH motif [10]. Expression of mini-N2G with point mutants in the CH domains abrogating actin binding, do not rescue. Thus, nesprin-2G's interaction with actin filaments is critical for nuclear movement in fibroblasts.

Strikingly, nesprin-2G accumulates along dorsal actin cables above the nucleus (Fig. 1B) during its movement in NIH3T3 fibroblasts and MEFs [9–11]. This result is based on colocalization of both endogenous nesprin-2G and expressed GFP-mini-N2G with dorsal actin cables [9–11]. In live cell movies, dorsal actin cables encountering the nuclear surface accumulate GFP-mini-N2G in minutes, forming linear arrays [10]. They also accumulate one of the two SUN proteins expressed in fibroblasts, SUN2, but not SUN1 or a number of other inner nuclear membrane proteins (Fig. 1B). Indeed, SUN2 is detected in linear arrays in primary MEFs as well [12]. Reflecting their morphology and actin-dependence, these LINC complex arrays have been termed transmembrane actin-associated nuclear (TAN) lines [10,11]. TAN lines form coincident with the initiation of nuclear translocation, move rearward with the nucleus and disassemble when nuclear movement ceases, providing direct correlative evidence for their involvement in the movement. This specific combination of LINC complex proteins in the nuclear envelope is required for TAN line formation and rearward nuclear translocation after LPA-stimulation and disrupting its components reduce NIH3T3 fibroblast migration speed into the wound [10,11].

2.2. Anchorage of TAN lines by the nucleus

The coincident movement of TAN lines and the nucleus implies that TAN lines are anchored to the nucleus to transmit the force that moves it. Studies show that proteins in both nucleoplasm and inner nuclear membrane contribute to nuclear anchorage of TAN lines. Unlike factors that are required for TAN line formation, disruption of these anchorage factors causes a novel phenotype in which the TAN lines form, but slip over an immobile nucleus.

Localization and interaction studies suggest that the nuclear lamina plays a key role in anchoring the LINC complex (Fig. 1B) [5,17]. There are three lamin genes encoding lamin B1, lamin B2 and A-type lamins. A-type lamins comprise three alternatively spliced isoforms: lamin A, lamin C and lamin C2 [18]. Among these, lamin A binds to SUN proteins via its C-terminus, whereas lamin B1 and lamin C bind to SUN proteins weakly [5,19]. MEFs null for A-type lamins, or NIH3T3 fibroblasts transiently knocked down for lamin A fail to move the nucleus or orient the centrosome after LPA stimulation [9]. While TAN lines still form in the A-type lamin disrupted cells, they slide over the nucleus instead of moving it, suggesting an anchorage defect. Consistently, diffusional mobility of mini-N2G and SUN2 measured by FRAP is increased in MEFs lacking A-type lamins [20].

Additional proteins in the nuclear envelope may assist in TAN line anchoring. One is Samp1/NET5, an inner nuclear membrane protein homologous to yeast Ima1, which is required for LINC

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