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Cytoskeletal tension induces the polarized architecture of the nucleus

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ABSTRACT

The nuclear lamina is a thin filamentous meshwork that provides mechanical support to the nucleus and regulates essential cellular processes such as DNA replication, chromatin organization, cell division, and differentiation. Isolated horizontal imaging using fluorescence and electron microscopy has long suggested that the nuclear lamina is composed of structurally different A-type and B-type lamin proteins and nuclear lamin-associated membrane proteins that together form a thin layer that is spatially isotropic with no apparent difference in molecular content or density between the top and bottom of the nucleus. Chromosomes are condensed differently along the radial direction from the periphery of the nucleus to the nuclear center; therefore, chromatin accessibility for gene expression is different along the nuclear radius. However, 3D confocal reconstruction reveals instead that major lamin protein lamin A/C forms an apically polarized Frisbee-like dome structure in the nucleus of adherent cells. Here we show that both A-type lamins and transcriptionally active chromatins are vertically polarized by the tension exercised by the perinuclear actin cap (or actin cap) that is composed of highly contractile actomyosin fibers organized at the apical surface of the nucleus. Mechanical coupling between actin cap and lamina through LINC (linkers of nucleoskeleton and cytoskeleton) protein complexes induces an apical distribution of transcription-active subnucleolar compartments and epigenetic markers of transcription-active genes. This study reveals that intranuclear structures, such as nuclear lamina and chromosomal architecture, are apically polarized through the extranuclear perinuclear actin cap in a wide range of somatic adherent cells.

1. Introduction

Accumulating evidence suggests that the three-dimensional organization of the nucleus regulates gene expression through lamina–chromosome interactions. The nuclear lamina is a thin filamentous meshwork that provides mechanical support to the nucleus and regulates essential cellular processes such as DNA replication, chromatin organization, cell division, and differentiation [1–3]. Imaging using fluorescence and electron microscopy has long suggested that the nuclear lamina is composed of structurally different intermediate filamentous lamin proteins (e.g., A-type lamins A and C and B-type lamins B1 and B2) [4] and nuclear lamin-associated membrane proteins (e.g., lamin associated peptides and emerins) that together form a thin shell largely confined to a narrow region underneath the nuclear envelope with a few filamentous structures extending to the intranuclear space [1,5]. Isolated horizontal imaging sections by confocal laser scanning microscopy through the middle of the nucleus seem to confirm this impression [1,6,7]: nuclear lamin proteins would form a thin layer that is spatially isotropic with no apparent difference in molecular content or density between the top and bottom portions of the nucleus in adherent cells. Such isotropic distribution of nuclear lamins, without any vertical polarization, is now conventional wisdom. Moreover, chromosomes are known to be condensed differently along the radial direction from the periphery of the nucleus to the nuclear center [8–11]; therefore, chromatin accessibility for gene expression is different along the nuclear radius [12,13]. However, close comparison of confocal sections along the vertical axis of the nucleus indicates that the major lamin protein lamin A/C is dominantly localized at the apical and lateral surfaces of the nucleus, and largely absent from its basal section.

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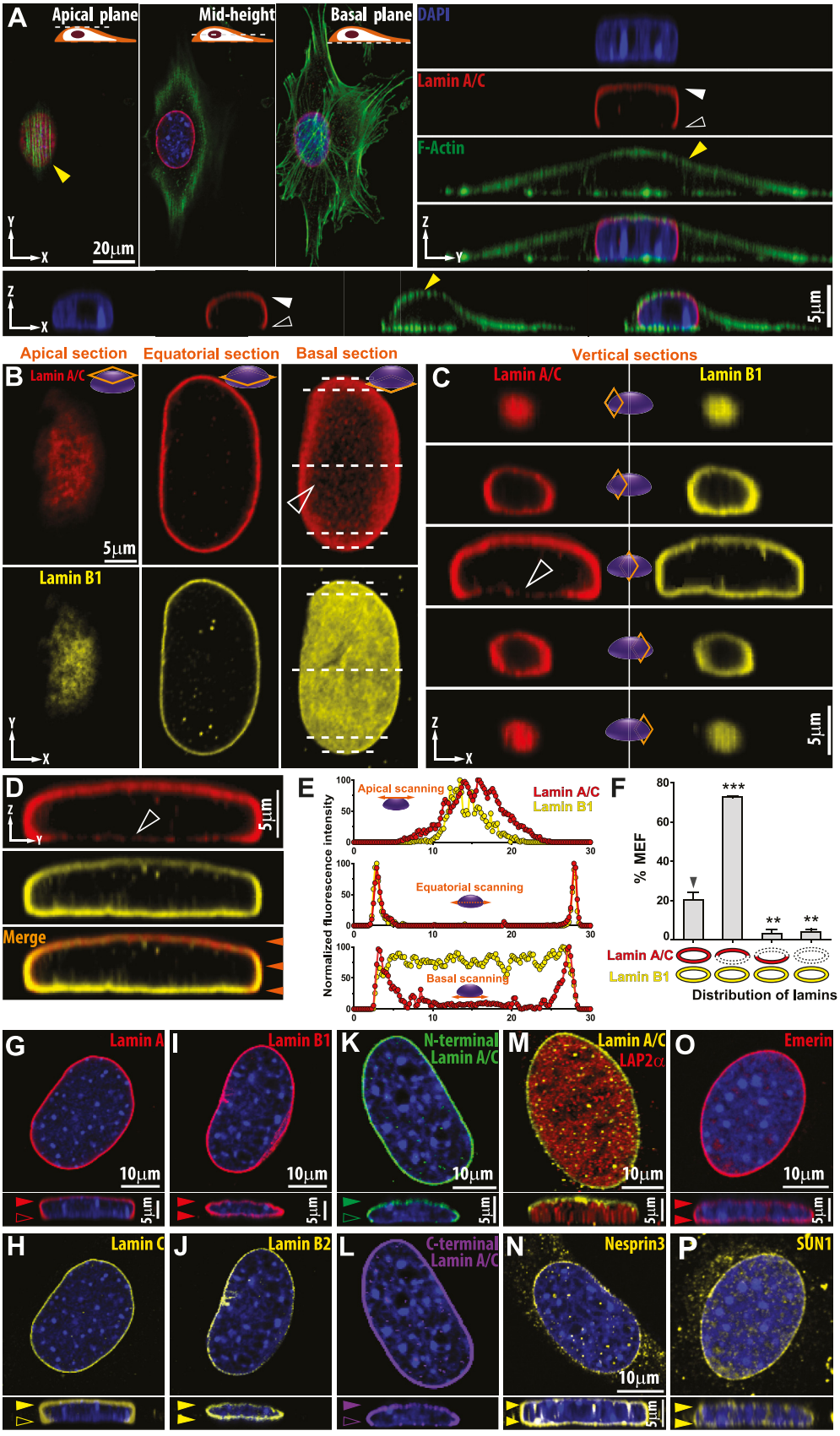

Fig. 1. The nuclear lamina is vertically polarized in adherent cells. A. Three-dimensional reconstruction of immunofluorescence confocal images of an adherent mouse embryonic fibroblast (MEF). Representative confocal sections along the apical, equatorial, and basal surfaces (i.e., XY planes) of the MEF stained for nucleus (blue), actin (green), and lamin A/C (red) reveals vertically distinct organization of actin filaments and lamin A/C. Cross-sections along the YZ and XZ planes of 3D-reconstructed captured images reveal apically polarized Frisbee-like distribution of lamin A/C and actin-cap fibers connecting from the basal surface of the cell to the apical surface of the nucleus. Full and empty white