Trends in Cell Biology

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Review

# Chromosome Intermingling: Mechanical Hotspots for Genome Regulation

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**Cells sense physical and chemical signals from their local microenvironment and transduce them to the nucleus to regulate genomic programs. In this review, we first discuss different modes of mechanotransduction to the nucleus. We then highlight the role of the spatial organization of chromosomes for integrating these signals. In particular, we emphasize the importance of chromosome intermingling for gene regulation. We also discuss various geometric models and recent advances in microscopy and genomics that have allowed access to these nanoscale chromosome intermingling regions. Taken together, the recent work summarized in this review culminates in the hypothesis that chromosome intermingling regions are mechanical hotspots for genome regulation. Maintenance of such mechanical hotspots is crucial for cellular homeostasis, and alterations in them could be precursors for various cellular reprogramming events, including diseases.**

## Trends

Microenvironment signals are transmitted to the cell nucleus via both physical and biochemical intermediates.

The spatial organization of chromosomes is critical to regulating microenvironmental control of gene expression.

Intermingling regions between chromosomes are enriched with transcription factors and RNA Pol II.

The functional clustering of genes is modulated by microenvironmental signals to exhibit differential gene expression programs.

## Introduction

Cellular differentiation programs result in a few hundred different cell types with well-defined transcription profiles. In this process, cells adapt to the tissue microenvironment and simultaneously sculpt it, thereby defining its geometry, rigidity, and mechanosensitivity [1–4]. Cells seamlessly transition through the epigenetic landscape during differentiation and *trans*-differentiation programs. These transitions are initiated at the molecular level: cells sense the geometry and stiffness of the microenvironment and perceive several biochemical signals via proteins on the cell membrane [5–7]. These signals are transduced to the nucleus via several canonical signaling pathways [8,9]. In addition, the nucleus is linked with an elaborate meshwork of cytoskeletal filaments, including actin, microtubules, and intermediate filaments, that bridges the extracellular microenvironment with the nuclear envelope and the genome [10–12]. The chemical and physical signals that reach the nucleus are translated via chromatin-remodeling enzymes and the transcription machinery to facilitate spatial control of gene expression [13–15]. Recent studies are beginning to reveal that the 3D neighborhoods of chromosomes, their degree of intermingling, and the clustering of genes within those intermingled regions, are optimized for cell type-specific regulatory programs [16–20].

In this review, we highlight our current understanding of how physical and chemical signals are transduced to the nucleus, how these signals are integrated within the 3D organization of chromosomes, and how cellular and nuclear responses to such signals remodel the nanoscale intermingling regions between chromosomes (Figure 1). Access to such nanoscale chromosome intermingling regions is made possible through several technological innovations in super-resolution microscopy, chromosome capture methods, and large-scale genome sequencing. Our synthesis of the recent work presented in this review culminates in the

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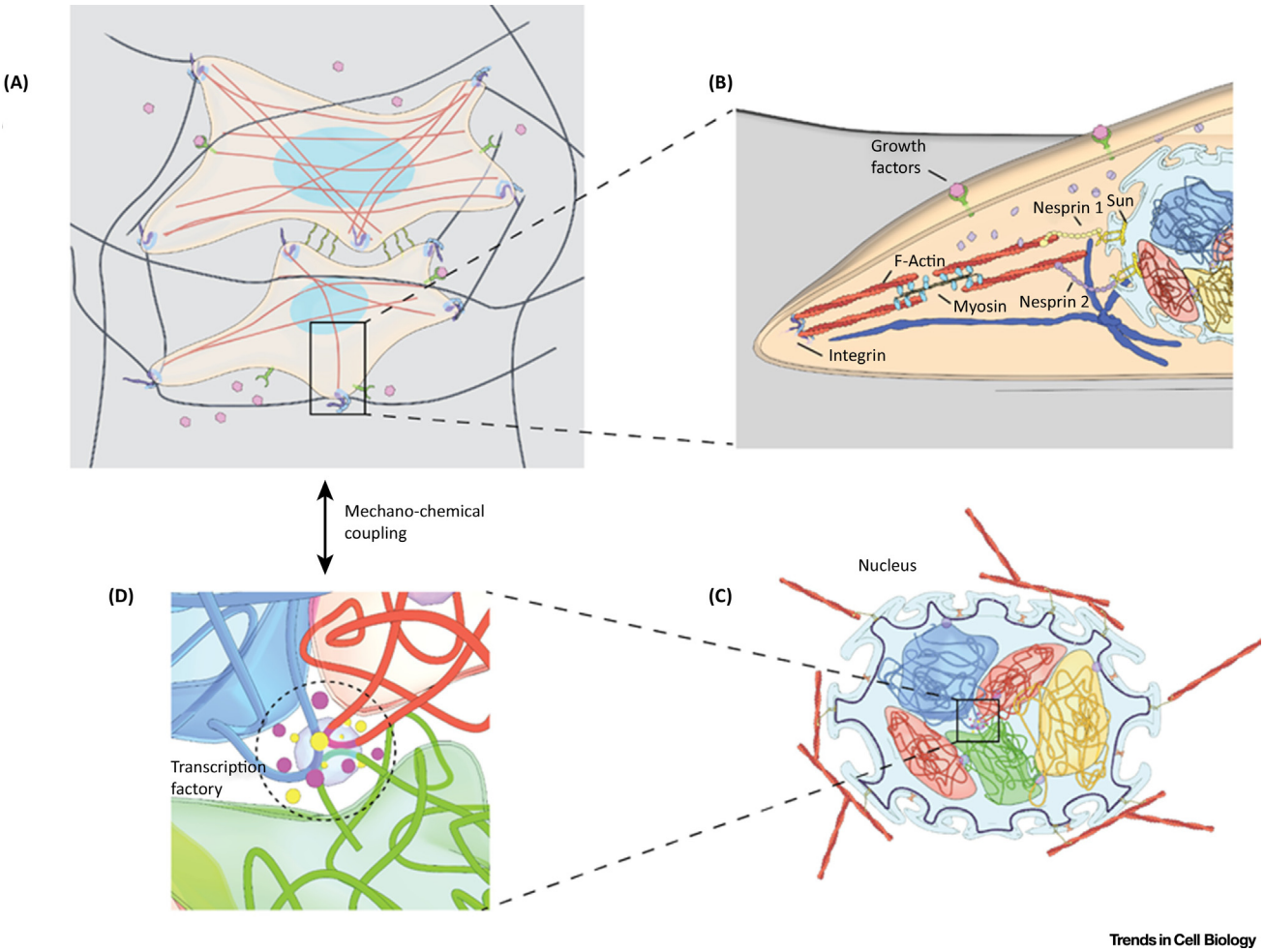


Figure 1. Mechanotransduction to the Cell Nucleus. (A) Cells sense the geometry and rigidity of the tissue microenvironment and perceive several biochemical signals via proteins on the cell membrane. (B) These signals are transduced to the nucleus via several canonical signaling pathways. In addition, the nucleus is linked with the cell membrane through an elaborate meshwork of cytoskeletal filaments, including actin, microtubules, and intermediate filaments. (C) The spatial organization of chromosomes in the cell nucleus, in particular the spatial neighborhoods of chromosomes, their degree of intermingling, and the clustering of genes within those intermingled regions, are optimized for cell type-specific regulatory programs. (D) The chemical and physical signals that reach the nucleus are translated via chromatin-remodeling enzymes and the transcription machinery to facilitate the regulation of particular genes. Our hypothesis is that these chromosome intermingling regions serve as mechanical hotspots that harbor cell type-specific gene clusters and integrate microenvironmental signals for genome regulation.

hypothesis that the chromosome intermingling regions are mechanical hotspots for genome regulation that harbor cell type-specific gene clusters. Going forward, we highlight the importance of rigorous theoretical models to understand cell type-specific chromosome packing and how gene regulatory networks couple with such spatial hubs to bring about precise genomic programs when subjected to different microenvironmental inputs.

## Mechanotransduction of Extracellular Signals to the Nucleus

In addition to soluble signals, such as cytokines or growth factors, cells experience mechanical signals in the tissue microenvironment, such as stretch, compression, or shear [21]. These mechanical signals are either static or cyclic, ranging from seconds to hours [22]. Force magnitudes can range from piconewtons for shear forces to nanonewtons for compressive loading in tissues. Mechanical and biochemical inputs are sensed via specialized membrane proteins, such as stretch activated channels, RTKs, integrins, GPCRs and a host of other