How genes find their way inside the cell nucleus

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Recent progress in live cell imaging suggests a role for nuclear actin in chromatin movement. In this issue, for the first time, a gene locus moving toward a subnuclear compartment was tracked. Motion of the locus is actin dependent, raising the question of whether chromatin movements are random or directed.

The genome of eukaryotic cells is dynamically packed inside the nucleus (for review see Fraser and Bickmore, 2007). Depending on their activity status, genes change position relative to defined subnuclear domains. Upon activation, genes move away from silencing heterochromatic regions and associate with other active genes in transcription factories. Many active genes are positioned in close proximity to the nuclear speckle compartment, which is enriched in splicing factors. Other active genes, including histone and small nuclear RNA (snRNA) genes, associate specifically with the Cajal body (CB), a domain involved in the biogenesis of small RNP (Cioc and Lamond, 2005; Stanek and Neugebauer, 2006). Although the reasons for such preferential associations are not known, Dundr et al. (see p. 1095 of this issue) show that interfering with the function of nuclear actin blocks movement of U2 snRNA gene loci toward CBs.

A ground-breaking tool to visualize chromatin movements in living cells consists of tagging the locus of interest with lac operator sequence repeats that can be monitored with a fluorescent protein fused to the lac repressor (Robinett et al., 1996). Using this approach, the Belmont laboratory reported long-range chromatin movements exceeding 1 μm along curvilinear trajectories (Chuang et al., 2006). Chuang et al. (2006) further discovered that nuclear actin and myosin are involved in chromatin mobility, as the repositioning of a chromatin locus was significantly delayed in cells transfected with mutant forms of either nuclear myosin I or actin. A nonpolymerizable mutant actin completely abolished locus redistribution, whereas a mutant that stabilizes filamentous actin completely abolished locus redistribution, raising the question of whether chromatin movements are random or directed.

In the study by Dundr et al. (2007), cell lines were constructed containing inducible arrays of U2 snRNA genes flanked by lac operator repeats. Distinct fluorescent proteins fused to the lac repressor and the CB marker protein coilin allowed simultaneous visualization of U2 snRNA genes and CBs, respectively. Although transcriptionally silent U2 genes did not associate with CBs, after the activation of transcription, the distance separating U2 genes from CBs progressively decreased until a stable association was formed. A novel directional tracking analysis method revealed that inactive U2 genes were relatively static, whereas activated gene arrays moved toward the nearest CB. Consistent with previous observations (Chambeyron and Bickmore, 2004; Chuang et al., 2006), activation of transcription was accompanied by repositioning of the U2 genes that looped out the corresponding chromosome domain (Dundr et al., 2007). Expression of a nonpolymerizable actin mutant abolished both association of the locus with CBs and repositioning relative to the chromosome domain (Fig. 1).

Together, the studies by Chuang et al. (2006) and Dundr et al. (2007) raise the dilemma of whether chromatin movements are active and directed. Indeed, both studies are compatible with the view that nuclear actin and myosin provide molecular motors that drive gene mobility and direct movement toward a target region in the nucleus, either the nuclear interior (Chuang et al., 2006) or a CB (Dundr et al., 2007). Nevertheless, an alternative scenario should be considered. There is compelling evidence implicating nuclear actin in chromatin remodeling and transcription (Bettinger et al., 2004; de Lanerolle et al., 2005). Therefore, actin may be required to relax chromatin structure, allowing an activated locus to loop outside of the chromosome domain. Chromatin loops from either the same or different chromosomes intermingle in the nucleus (Branco and Pombo, 2006), which is consistent with a model of random chromatin motion constrained by tethering at the base of the loop and interchromatin molecular crowding. According to such a self-organization model, diffusing chromatin loops may collide stochastically with neighboring compartments until specific molecular interactions stabilize a defined association (Misteli, 2007). It is noteworthy that Dundr et al. (2007) observed significant oscillations between U2 genes and CBs before the establishment of a stable association, which argues against a strictly directed movement. In further agreement with the self-organization model, the stable association between U2 genes and CBs requires U2 snRNA transcripts (Frey and Matera, 2001; Dundr et al., 2007) that most likely interact with snRNA-binding proteins highly enriched in CBs.

Ultimately, Dundr et al. (2007) have demonstrated that the association between U2 genes and CBs results from actin-dependent long-range chromatin movements toward the CB.
An important implication of this work is the need to develop new methods to separate and molecularly characterize the role of actin in chromatin structure and gene mobility.

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References

Bettinger, B.T., D.M. Gilbert, and D.C. Amberg. 2004. Actin up in the nucleus. Nat. Rev. Mol. Cell Biol. 5:410–415.

Branco, M., and A. Pombo. 2006. Intermingling of chromosome territories in interphase suggests role in translocations and transcription-dependent associations. Proc Biol Sci 273: e138.

Chambeyron, S., and W.A. Bickmore. 2004. Chromatin decondensation and nuclear reorganization of the HoxB locus upon induction of transcription. Genes Dev. 18:1119–1130.

Chuang, C.H., A.E. Carpenter, B. Fuchsova, T. Johnson, P. de Lanerolle, and A.S. Belmont. 2006. Long-range directional movement of an interphase chromosome site. Curr. Biol. 16:825–831.

Cioce, M., and A.I. Lamond. 2005. Cajal bodies: a long history of discovery. Annu. Rev. Cell Dev. Biol. 21:105–131.

de Lanerolle, P., T. Johnson, and W.A. Hofmann. 2005. Actin and myosin I in the nucleus: what next? Nat. Struct. Mol. Biol. 12:742–746.

Dundr, M., J.K. Ospina, M.-H. Sung, S. John, M. Upender, T. Ried, G.L. Hager, and A.G. Matera. 2007. Actin-dependent intranuclear repositioning of an active gene locus in vivo. J. Cell Biol. 179:1095–1103.

Fraser, P., and W. Bickmore. 2007. Nuclear organization of the genome and the potential for gene regulation. Nature. 447:413–417.

Frey, M.R., and A.G. Matera. 2001. RNA-mediated interaction of Cajal bodies and U2 snRNA genes. J. Cell Biol. 154:499–509.

Misteli, T. 2007. Beyond the sequence: cellular organization of genome function. Cell. 128:787–800.

Robinett, C.C., A. Straight, G. Li, C. Willhelm, G. Sudlow, A. Murray, and A.S. Belmont. 1996. In vivo localization of DNA sequences and visualization of large-scale chromatin organization using lac operator/repressor recognition. J. Cell Biol. 135:1685–1700.

Stanek, D., and K.M. Neugebauer. 2006. The Cajal body: a meeting place for spliceosomal snRNPs in the nuclear maze. Chromosoma. 115:343–354.

Figure 1. Activation of a tandem array of U2 genes results in repositioning of the locus that loops out of the chromosome domain. [A] In the presence of wild-type actin, the chromatin loop associates with a CB either by constrained diffusion or directed movement. [B] Expression of a dominant-negative nonpolymerizable mutant actin abolishes both looping of the locus outside of the chromosome domain and association with CBs.