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Gene activation at the edge of the nucleus

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The position of a gene within the nucleus can be a determinant of the level of gene activity. In recent years, particular emphasis has been placed on the nuclear envelope as a transcriptionally silent nuclear location. A provocative study on the relationship between nuclear architecture and transcription of the HIV provirus, published in this issue of *The EMBO Journal*, warrants a broader view.

When we observe order in cells we search for the reasons behind it, a behaviour derived, in part, from the first days when we learned about cytoplasmic compartments. This is also exemplified in thinking about chromatin organization in the eukaryotic nucleus. When the early view of a disorganized bowl of spaghetti surrounding a nucleolus morphed into the current textbook view, a functional order in the nucleus became possible too, even without membranes to delineate compartments. The nucleolus is still in the middle (not actually true in many cells) but chromatin organization is non random. Heterochromatin lines the inner surface of the nuclear envelope and the more open, transcriptionally active euchromatin is dispersed in the nuclear interior. The natural assumption was that order in the nucleus must facilitate gene regulation. Genes move to the periphery (to heterochromatin) for switching off, and move internally into euchromatin for switching on. This view gained traction after a demonstration, in budding yeast, that gene silencing can be facilitated by artificially tethering the loci to the nuclear envelope (Andrulis *et al*, 1998).

However, the early years of this decade proved troublesome for functional models of chromatin organization. Tethering experiments were not initially possible in mammalian cells, and measurements of chromatin dynamics indicated a predominantly sub-micron range motion of interphase chromatin (Levi and Gratton, 2008), limiting the environments that loci can access in mammalian nuclei, often 10–20 μm in diameter. Measurement of nuclear protein dynamics showed that many regulatory proteins have relatively free access to all areas of the nucleus (Cheutin *et al*, 2003). How can the environment or the localization of a gene matter if the movement of regulatory factors is unlimited and genes are immobile?

Well, mitosis affords the potential for large-scale chromatin reorganization (Thomson *et al*, 2004), and even if dynamic, observed differences in protein accessibility between nuclear domains should allow the microenvironment to matter. Indeed, high protein mobility allows new microenvironments to be nucleated in minutes (Muramoto and Chubb, 2008). Finally, tethering experiments were performed in mammalian cells, and as in initial yeast experiments, silencing was administered, albeit in a leaky fashion, by peripheral localization (Finlan *et al*, 2008; Reddy *et al*, 2008). Another study, tethering an artificial locus, found no repression (Kumaran and Spector, 2008), but the locus was heterochromatic, perhaps masking silencing effects of a peripheral localization.

However, new work from the Marcello laboratory, published in this issue of *The EMBO Journal* (Dieudonne *et al*, 2009) demands a wider perspective. Their study compared the subnuclear position of an HIV provirus in induced and non-induced states, in several human cell lines. Before induction, the provirus resides in a peripheral position, often associated in trans with heterochromatin on chromosome 12. Upon induction, the trans association was lost, but the peripheral localization retained. The study showed, using a combination of RNA FISH and live imaging of fluorescently labelled RNA that most transcription of the provirus occurs close to the nuclear envelope.

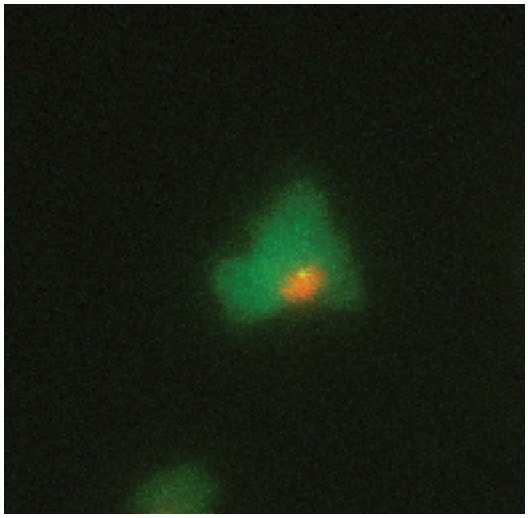

Figure 1 Visualizing transcription at the edge of the nucleus. Nascent RNA from a single gene is visualized as a fluorescent green spot above the red nuclear background. Nascent RNA visualized by tagging an endogenous locus in *Dictyostelium* cells with 24 MS2 repeats and expression of an MS2–GFP fusion protein. Nucleus marked with a fusion of RFP and histone H2B. Image courtesy of Tetsuya Muramoto.

Putting aside the thorny issue of judging where exactly the edge of the nucleus is, HIV may be naturally well suited to avoid normal positional control. Another contribution may come from proviral insertion sites, which could provide immunization against peripheral silencing. It is worth noting that other experiments in yeast have reported stimulation of gene expression by peripheral tethering, and other studies have detected transcription at the nuclear envelope (Towbin *et al*, 2009) (Figure 1). The nuclear envelope is far from uniform in its effects. The place matters less then its contents. Obvious structural landmarks, such as the nuclear envelope, may be less important than the environment at the landmark. Structural landmarks can be promiscuous in their associations, apparent in recent work on nocturnal retina rod cells showing inversion of the textbook nucleus, with euchromatin outside and heterochromatin central. The inversion seems to be a strategy to minimize light scattering in the eye (Solovei *et al*, 2009). The reasons for order can surprise us in the most beautiful ways.

It is hard to see how nuclear positioning can be wholly dictatorial. Given the free movement of many transcription factors throughout the nucleus, no gene is an island. If chromatin does not move much, strong positional effects on the wrong genes would damage cell adaptation. With overwhelming nuclear position effects, what would happen to neighbouring genes that need opposite regulation (Morey *et al*, 2009)? Contributions to regulation come from many sources. The question we must ask now is not whether nuclear architecture can influence gene regulation—it is clear that it can. We must learn when it does.

Conflict of interest

The authors declare that they have no conflict of interest.

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