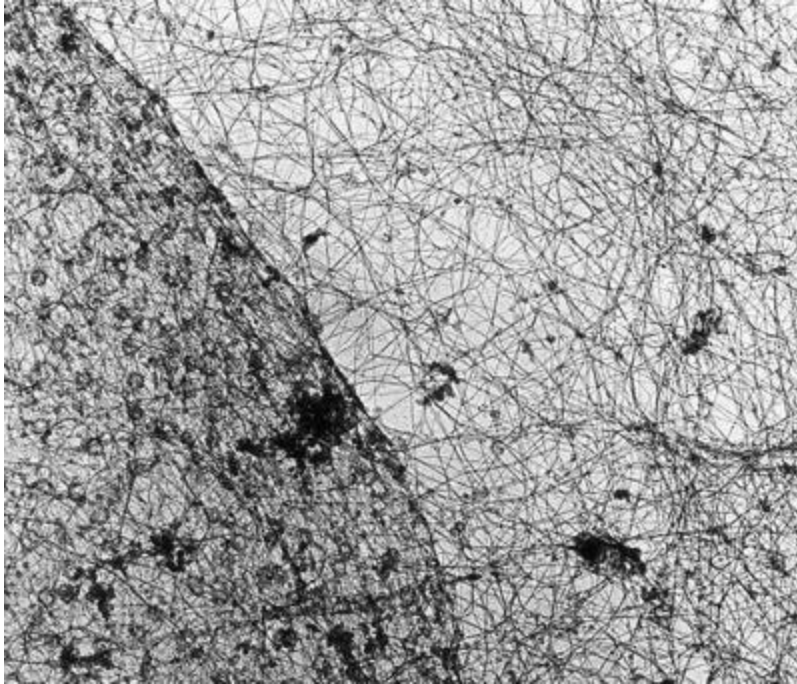


# The Nuclear Envelope's Role in Gene Regulation

Within the nucleus, the replicative enzymes must somehow find their sites for initiating DNA synthesis; the transcription factors and polymerases must find their promoters and enhancers; the RNA-processing factors must find their RNA-splicing sites; and the messenger RNA must efficiently find the pores through which to exit the nucleus. This is a great deal to ask of molecules in solution. It follows that we would expect the various factors involved in transcription to be floating around in the nuclear sap, bumping randomly into DNA. The RNA so formed would then be spliced and bump around the nucleus until it found a nuclear pore through which to leave.

An alternative model suggests that RNA is transcribed on a solid substrate in which all the enzymes needed for transcription, processing, and transport are collected together (see Schneider and Grosschedl 2007). There are precedents for thinking in such terms. The electron transport chain of the mitochondria is such an ordered aggregate, and the DNA-synthetic enzymes of bacteria have long been known to reside on the inner surface of the cell membrane. Indeed, the nuclear envelope appears to be the location where DNA replication is regulated (Infante et al. 1971; Anderson et al., 2012). What one has to ask, then, are the following two questions: 1. Is the nuclear envelope a substrate that recruits transcriptional regulators, and 2. is this a place where specific genes bind during development?

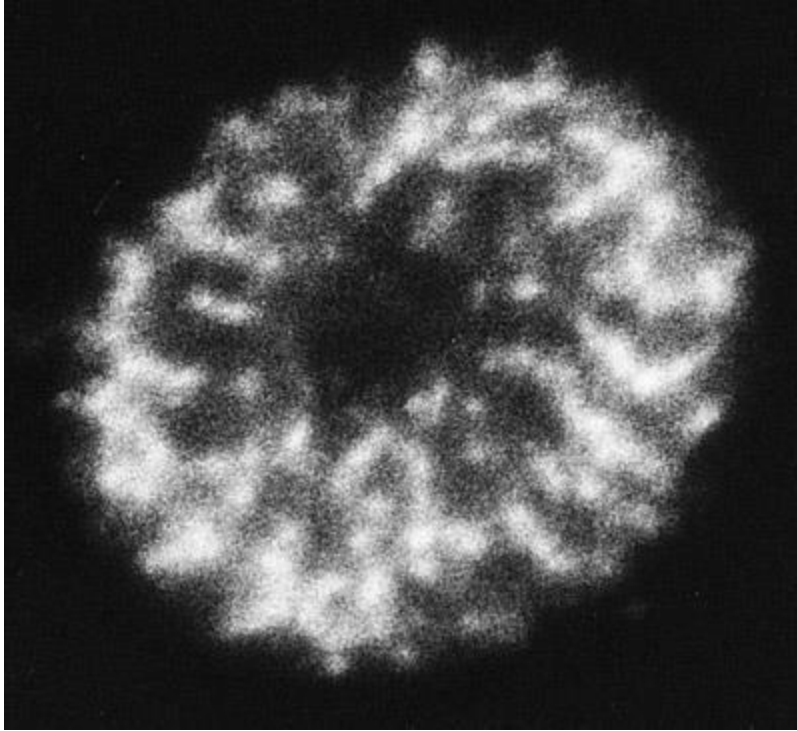
A nuclear matrix can be isolated by dissolving nuclei in lipid detergents and solubilizing most of the DNA with DNases (Wilson 1895; Berezney and Coffey 1977; Capco et al. 1982). Transmission electron microscopy of such complexes shows a meshwork of proteins that extends throughout the nucleus and connects to the cytoskeleton at the nuclear envelope (Figure 1).



**Figure 1** Transmission electron micrograph (47,000 $\times$ ) of a portion of nuclear matrix (left) and surrounding cytoplasm. Cytoskeletal filaments are clearly visible. The mouse fibroblast cells were extracted with detergent to remove lipids and further treated with DNase I. In 1895, E. B. Wilson, looking through the light microscope, reported that the nucleus was traversed by fibers that were continuous with those of the cytoplasmic reticulum and that surrounded the chromatin. (From Capco et al. 1982, courtesy of S. Penman.)

When one isolates such a matrix, DNase has removed about 98 percent of the DNA. The DNA that is still bound to this matrix (and presumably protected from the DNase, as it is so tightly associated with it) appears to be enriched for actively transcribing genes. The ovalbumin gene is preferentially associated with the nuclear matrix in adult chick oviduct cells, but not in chick liver or erythrocyte cells. The globin genes, moreover, are not associated with the nuclear matrix of the oviduct cells (Robinson et al. 1982; Thorburn and Knowland 1993). Ciejek and coworkers (1983) confirmed and extended these observations, showing that the entire hormone-inducible transcription unit of the ovalbumin gene is bound to the nuclear matrix. No other genes within 100,000 base pairs of this unit are matrix-associated. Moreover, when estrogen (which is necessary for inducing the ovalbumin genes) was withdrawn from the animals, the specific attachment of these genes to the nuclear matrix was abolished. It appears that these genes are bound to the nuclear matrix only when activated.

In 1985, Hutchinson and Weintraub showed that DNase I-sensitive sites are not found uniformly throughout the nucleus. They treated nuclei with DNase I, and then repaired the nicks with radioactive nucleotides. The labeled DNA should represent just the actively transcribing (i.e., DNase I-sensitive) genes. The results of such treatment showed that the DNase I-sensitive DNA existed at the periphery of the nuclei and along channels or fibers that connected to the nuclear envelope (Figure 2). It is possible, therefore, that active genes are specifically associated with the nuclear envelope or matrix.



**Figure 2** Presence of active chromatin along the nuclear periphery and channels. Erythrocyte nuclei were treated with DNase I, which is thought to nick actively transcribing chromatin regions. This nick was "healed" by nick translation within the nucleus in the presence of nucleotides whose presence could be detected by fluorescence. The labeled nucleotides were found at the periphery of the nucleus and along structures leading inward from the nuclear envelope. (From Hutchinson and Weintraub 1985.)

Another type of evidence for nuclear matrix participation in transcription involves the finding that most (some report 95 percent) of the newly-synthesized RNA appears to be attached to the nuclear matrix (Herman et al. 1978; Miller et al. 1978; van Eekelen and van Venrooij 1981; Marinlan al. 1982). This binding appears to be mediated by a set of nuclear matrix proteins. These proteins include lamin B1, a major component of the nuclear envelope (Ludérus et al. 1992) and the transcription factor YY1/NF-E1 that was found to be identical to nuclear matrix protein 1 (NMP-1) (Guo et al. 1995). Given that active genes, RNA polymerase, and nascent transcripts appear to be bound to a nuclear matrix, Jackson and Cook (1985) have proposed that transcription does not occur by a "mobile polymerase traveling down the length of a gene." Rather, they envision the RNA polymerase as tethered to the nuclear matrix, with the DNA traveling through it.

In 2008, several papers showed that they could repress or enhance the expression of different genes by tethering them to the nuclear lamina. Reddy et al. (2008) and Finlan et al. (2008) showed that attachment of chromatin to the nuclear envelope suppressed the expression of those genes near these sites. The suppression appeared to be due to histone deacetylases that were on the nuclear envelope. This has been subsequently confirmed in *Drosophila* nuclei, where HDAC1 appears to associate with B-type lamin proteins on the nuclear envelope (Milon et al. 2013). The molecular mechanism of this tethering and subsequent gene repression is also due to the binding of DNA to the nuclear lamins by the transcriptional repressor Krox (Zullo et al. 2012). Shimi and colleagues (2008) have shown that C-type lamin is associated with actively transcribing genes and that the nuclear envelope might have microdomains that suppress and activate transcription.

The nuclear pore complexes might also be critical in regulating gene expression. It is possible that different nucleoporin proteins (the 30 or so different proteins that construct the nuclear pores) are different in different cell types and change as the cell develops. D'Angelo and colleagues (2012)

showed that the nucleoporin Nup 210 is absent in proliferating muscle cell and neuron precursors, but becomes incorporated into the nuclear pore during muscle cell differentiation. If this protein is blocked, differentiation does not occur. This protein does not appear to affect the transport of genes out of the nucleus. Rather, it appears to be essential for the induction of those genes responsible for cell differentiation.

Thus, the nuclear envelope may be an important site for the regulation of DNA replication and transcription.

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