loop structures, called replicons, that are attached to the matrix at the loop bases. The replication machinery is located at the attachment sites, and when the DNA is copied the loops are pulled through the machinery.

But the matrix's influence on nuclear DNA organization apparently doesn't stop at the replicon level. The 50,000 replicons in the average mammalian genome are duplicated in clusters of 10 to 100, and recent work by Berezney's group, now at the State University of New York at Buffalo, and by Hiromu Nakamura and his colleagues at the Aichi Cancer Center in Nagoya, Japan, indicates that the nuclear matrix is needed to organize the replicon clusters. Berezney is also now able to pinpoint the coordinates for every single replication site. This may be useful, he says, in understanding how the nuclear architecture of normal and cancer cells differ, and how this may be related to the increased proliferation of cancer cells.

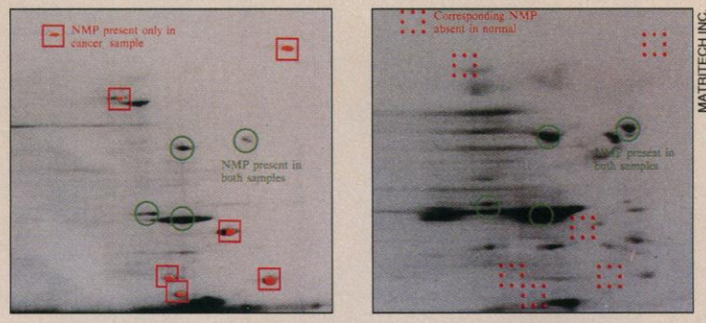
Impact beyond DNA

Of course, DNA replication is only one of the major biochemical reactions that takes place in the nucleus. The DNA of the genes also has to be copied into messenger RNAs, the necessary first step in protein synthesis. And since genes contain sequences that do not code for protein structure, these noncoding segments, called introns, must be spliced out of the mRNA molecules before they move out of the nucleus into the cell cytoplasm where protein synthesis actually takes place. And that's where the new work by the Lawrence group comes in, as it points to the locations in the nucleus where those reactions take place.

For reasons that aren't understood, after mRNAs are synthesized a long sequence of adenine nucleotides known as the poly(A) tail is added to one end. (Nucleotides are the building blocks of nucleic acids.) Since other forms of nucleic acids don't have a poly(A) tail, Lawrence and her colleagues reasoned that if they could find the nuclear localization of all the poly(A) tail-containing molecules, they would better understand the arrangement of mRNAs and the genes that encode them in the nucleus.

Looking for Cancer in Nuclear Matrix Proteins

Within the past decade, cell biologists have begun to work out the functional implications of the nuclear matrix, a network of structural proteins that permeates the nucleus and helps to maintain its shape. It also plays a role, they are finding, in regulating key reactions in the nucleus, such as gene activation (see main story). And further study of the matrix may lead to new methods of cancer detection and treatment as well. At least that's the optimistic view of officials at Matritech Inc., a small biotech company in Cambridge, Massachusetts.



MATRITECH INC.

Cancerous difference. Two-dimensional electrophoresis finds proteins in cancer cells *(left)* not seen in normal cells.

Already in the Matritech's pipeline are assays for detecting bladder, breast, colon, cervical, and several other cancers, which are based on findings that the protein composition of the nuclear matrix differs between cancer cells and their normal counterparts. The medical market for such assays is estimated at more than $1 billion per year, so it may seem surprising that, to date, Matritech has had the commercial nuclear matrix field mostly to itself. Part of the explanation for this is that for years researchers had essentially ignored nuclear matrix proteins (NMPs) because the insoluble proteins are extremely difficult to isolate and work with. "Until recently, most biochemists had thrown this stuff down the drain," says Graham Lidgard, vice president of product development at Matritech.

But while scientists have had trouble breaking the matrix down into its component parts, nature apparently achieves this with ease. In test-tube studies over the past few years, company researchers have been startled to find that as cells die, their nuclear matrix disappears and the matrix proteins are released into the surrounding fluids, whether this be in lab culture or in living animals.

This discovery opened up another line of inquiry: Researchers could compare the NMPs released by distinct types of cells to see if they were all the same or whether different cell types have their own distinct variants. Using monoclonal antibodies on cells in lab culture, Matritech has identified more than a dozen NMPs, many of them cell-specific. More important to Matritech's financial future, NMPs released by cancer cells differ from those released by normal cells of the same type. Indeed, in the latest issue of *Cancer Research*, a team from John Hopkins University School of Medicine, including Alan Partin and Donald Coffey, reports that prostate cancer cells carry a nuclear matrix protein not seen in normal prostate cells or even in "hyperplastic" prostate tissue that shows excessive cell growth but is still benign. Matritech hopes to detect proteins like that in simple blood or urine tests that use such standard lab procedures as two-dimensional electrophoresis to separate proteins according to their size and charge.

Cancer diagnostics based on that principle should begin clinical trials this year, according to Matritech officials, who believe their assays could be much more sensitive and specific than the few current tests on the market, many of which look for proteins found on a cancer cell's surface. Those assays, says Lidgard, often give too many false-positives, because the proteins they detect are released in conditions other than cancer. For example, one popular serum test to detect prostate cancer often turns up benign hyperplasia. Another cancer screening test, the Pap smear for cervical cancer, suffers from the opposite problem; the rate of false negatives is estimated at 25%. To tackle that problem, Matritech is developing an antibody assay for matrix proteins to supplement the traditional test that depends simply on observations of structural changes in cervical cells to diagnose potential cancers.

And that's not all: The company has just set up a new research group to begin exploring whether their nuclear matrix work could provide any new therapeutic strategies for cancer. It's still too early to know what those strategies might be, company researchers say, but they wouldn't be investing the money if they weren't optimistic. On the other hand, Matritech's scientific and financial success is far from assured. Cautions Shelia Taube, chief of the Cancer Diagnostic Branch at the National Cancer Institute: "I think [their tests] are reasonable approaches to try, but I don't think we have sufficient data at this point to say they will work."

–John Travis