

TRAFFICKING IN TRANSCRIPTION

Dissecting the intricacies of DNA transcription and transcription repair is likely to be key to treating many cancers and other diseases.

by Marilyn Davis



Sukesh Bhaumik prepares a solution for inserting genes inside cells.

All multicelled creatures rely on transcription for life. It's the process by which DNA in the cell's nucleus is copied into strands of RNA. Those RNA strands then must move out of the nucleus to be translated into proteins critical for cell activities.

For the cells in our various organs to function properly, certain genes must be transcribed at certain times. Each gene has a promoter sequence that signals where the gene begins, an "active" sequence that is copied, and a sequence that says where

to stop copying. Start, go, stop. It's like traveling from green light to red light.

But traffic isn't so simple, and neither is transcription. DNA gets damaged in the cell by all sorts of things, from sunlight to mutation-producing chemicals. That damage jams the transcription machinery. Down the line, the result can be various types of cancer or degenerative diseases. "No RNA, no protein," says Sukesh Bhaumik, an assistant professor of biochemistry and molecular biology. "The cell can transform into a diseased

cell because it lacks a particular protein."

Fortunately, cells can fix a gene's problem—most of the time. When the repair system fails, however, cells become abnormal.

Bhaumik and his students study these intricate cellular processes. It's an exciting, intriguing area of research that will lead to new disease treatments, he says.

To get transcription going, an activator protein binds to the promoter. That protein attracts other proteins, which then attract an enzyme called RNA polymerase II. The

polymerase starts moving down the gene, copying one of the strands as it goes.

The active parts of genes are wrapped around proteins called histone complexes, like beads on a string. As the RNA polymerase moves busily along, it recruits enzymes to put chemical groups on the histones and unwrap sections of the DNA so that it can be accessed and copied. But if the RNA polymerase runs into damaged DNA, it's like a wrench thrown into the works. The process stalls.

Luckily, the cell has a trick up its sleeve: In a process called transcription-coupled repair (TCR), other proteins repair the damage. This protein assemblage travels along with the RNA polymerase.

Bhaumik's lab has discovered that when RNA polymerase hits a snag, its largest component degrades. This somehow triggers disassembly of the entire polymerase complex, clearing the way for the TCR proteins to quickly fix the damaged site. Then a new cycle of transcription begins at the promoter, this time without the snag.

So the cell can't afford to do without its editor—its TCR mechanism. When TCR doesn't work right, it can lead to disease, such as various cancers, Parkinson's disease, and other diseases of aging. The defect in the repair system is likely to be present in multiple cells, and it's known that mutations in certain genes, such as the BRCA-1 breast cancer gene, cause defects in TCR.

What regulates the traffic that controls transcription-coupled repair? A whole network of proteins and enzymes is involved, much of it unknown.

"My lab is trying to understand the DNA factors (repair proteins) involved," Bhaumik says. "We know only a few. How are they recruited to the site? How do they interact and cross-talk? What happens first, second, third? Our lab has identified some of the factors, but we don't know all the players."

Most researchers in this area work with proteins and DNA in test tubes, Bhaumik

says. "But we are doing this in the living cell. It's much more difficult, but it gives us a much more real picture of what's going on.

"Answers would help [researchers] design drugs to treat diseases caused by defective TCR. If someone has defective TCR [leading to cancer], you could convert cancerous cells to normal cells by [fixing] transcription-coupled repair."

Bhaumik's lab has discovered certain DNA factors involved in transcription and transcription-coupled repair. These discoveries and others like them may eventually lead to scientists being able to tailor drug treatments that target only cancer cells.

If TCR doesn't do its job, something is amiss with one of the proteins involved in the repair mechanism. To find what's wrong, Bhaumik's lab induces multiple mutations in proteins known to be involved in repair, then sees how that affects things down the line. If no repair takes place, they can hone in on the protein mutation that's the culprit. The idea is that eventually other scientists can use that information to develop drug therapies.

Bhaumik and his students are looking not just at transcription-coupled repair, but at how histone modification goes wrong, which also can lead to cancer. In treating prostate cancer and multiple myeloma, researchers combining histone modification drugs with conventional cancer drugs are getting much better results than with the conventional drugs alone, Bhaumik says. This so-called combinatorial therapy may be the wave of the future in treating cancer and other diseases.

"It will have a huge impact," he says.

For more information: Dr. Sukesh Bhaumik, sbhaumik@siu.edu. Work in Bhaumik's lab is funded by the Mallinckrodt Foundation, the American Cancer Society, and the American Heart Association. Abhijit Shukla, a doctoral student of Bhaumik's who is now a postdoctoral fellow at Harvard Medical School, also had funding from the AHA and was named co-Outstanding Graduate Student Researcher in 2007.



Bhaumik with his lab team: graduate students Priyasri Chaurasia, Abhijit Shukla, Geetha Durairaj, Shweta Lahudkar, and Shivani Malik.