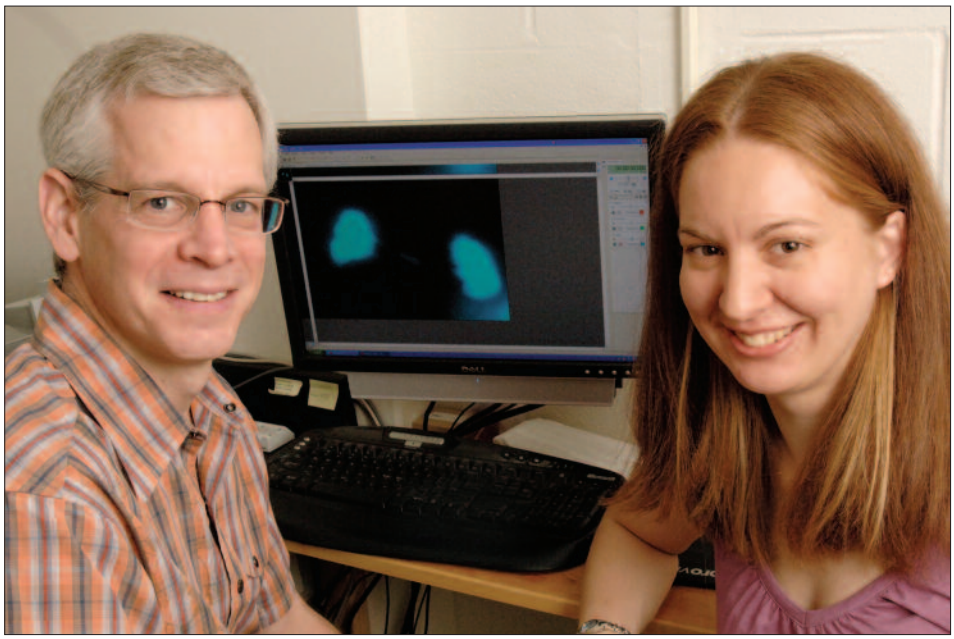
Tug-of-war proves deadly in cancer cells, DMS researchers find

On occasion, a tug-of-war can turn deadly. Certainly a figurative version of the playground game can have lethal repercussions. A recent Dartmouth study showed that when cancer cells wage what amounts to a tug-of-war, it can result in a mismatch of chromosomes. Dartmouth biochemist Duane Compton, Ph.D., and molecular and cellular biology graduate student Sarah Thompson recently reported the finding in the *Journal of Cell Biology*. Their study was also featured in the journal's "Comment" and "In This Issue" sections.

Human cells have 46 chromosomes arrayed in 23 pairs. Many tumor cells, however, have too few or too many—a state called aneuploidy—yet they still manage to grow. Normally, as a cell reproduces, it goes through mitosis and splits into two genetically identical cells.



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Biochemist Duane Compton, left, and graduate student Sarah Thompson made videos of tumor cells dividing.

Dance: Mitosis is a perfectly timed, intricate dance: DNA strands in the nucleus gather into chromosomes and double; the membrane surrounding the nucleus disappears; organelles called centrioles move to opposite sides of the cell, stretching spindle fibers between them; the chromosomes line up as pairs of sister chromatids along the spindle fibers; the fibers pull the chromatids to opposite poles of the cell; each set of chromatids becomes the chromosomes in a daughter cell; a nuclear membrane forms around each new set of chromosomes; and, finally, the cell membrane pinches the cell in half, forming two identical daughter cells. The process repeats itself again and again.

Compton points to a lagging chromatid in one of his videos.

But sometimes the chromosomes missegregate during the dance and wind up in the wrong daughter cell. Such aneuploid cells usually die—unless they are tumor cells. Those manage to propagate all too readily.

Scientists used to think that missegregation happened when the timing mechanism was off, causing cells to divide early, before all the chromosomes were properly aligned. Most cancer biologists look at dead cells under a microscope. But Compton and Thompson videotaped live human cancer cells—breast, colon, and lung—as they were actually dividing. The researchers were surprised to discover that, in these tumor cells at least, the timing was fine. Instead, the chromosomal reshuffling occurred because some chromatids remained attached to spindle fibers from both sides of the cell.

"So what's happening is when the chromosomes move apart, this one doesn't know which direction to go." Compton points to a lagging chromatid in one of his videos. "You can see this one's being tugged in both directions. . . . It's stuck in a tug-of-war."

Defect: The researchers not only pinpointed the defect but have figured out a way to force otherwise normal cells to missegregate their chromosomes. The nontumor aneuploid cells failed, however, to keep dividing. Still, the researchers think that being able to reproduce the instability may help them identify how to reverse it.

Chromosomal instability in tumor cells lets the cells shuffle their genes around constantly and "acquire new traits that allow them to grow in new environments, metastasize, or take on drug resistance," explains Compton. "If we can make them stable, that forces them into one and only one state." And that, he adds, will offer "a better chance of being sensitive to specific chemotherapeutic agents."

Some leads: Next, Compton and Thompson want to determine how aneuploid tumor cells keep their mismatched chromosome sets. They already have some leads about how to control the instability. They expect to publish those findings in the coming year.

They are also setting up collaborations with researchers at Dartmouth's Norris Cotton Cancer Center to investigate whether chromosomal instability contributes to the formation of tumors as well as to their growth.

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