

Safeguards to Ensure Genetic Fidelity

Accurate maintenance of a cell's genetic material during cell division is crucial to ensuring that genetic defects capable of fueling abnormal cell growth are not passed on to daughter cells. CCR scientists are studying the proteins necessary for ensuring proper DNA content.



(Image: Jan Wisniewski and Carl Wu, CCR)

Binding of a novel protein, Scm3 (green), to the histone Cse4 (red) in the cell nucleus helps chromosomes properly segregate during cell division. Errors in segregation can promote cancer or, during development, congenital birth defects. White appears where the two proteins bind together.

Separating Chromosomes during Cell Division

In eukaryotes, failures in proper chromosome duplication and segregation during cell division can result in cancer or congenital birth defects. So a DNA-protein superstructure, called a kinetochore, assembles just in time to separate chromosome pairs and link each to microtubules that move them away from one another. Understanding the complex mechanisms that guarantee accurate chromosomal separation may lead to potential new therapeutic interventions.

Carl Wu, Ph.D., Head of the Chromosome Structure and Gene Regulation Section of the Laboratory of Biochemistry and Molecular Biology at CCR, leads a team of scientists who study kinetochore assembly. A paper published in the June, 2007, issue of *Cell* by lead authors Gaku Mizuguchi, Ph.D., and Hua Xiao, Ph.D., senior scientists in Wu's laboratory, describes a novel protein, Scm3, that is required for

kinetochore formation in yeast. Usually proteins called histones keep DNA neatly coiled around them when cells are not dividing, but when the time for separation arrives, the nonhistone Scm3 displaces some histones so it can bind directly to one called Cse4. This dynamic action sets the stage for the kinetochore's assembly and allows chromosome segregating activity to begin to occur.

Although the protein sequence of Scm3 is evolutionarily conserved only in fungi, a human equivalent to Scm3 may exist, which could be an exciting new clinical target for interfering with the highly aberrant cell division seen in many forms of cancer.

Reining in Broken DNA

The same method of gene rearrangements that allows lymphocytes to create an arsenal of immune responses can potentially lead to aberrant DNA breakage and genetic instability. Andre Nussenzweig, Ph.D., of the Experimental Immunology Branch at CCR,

and his brother Michel Nussenzweig, M.D., Ph.D., of the Laboratory of Molecular Immunology at Rockefeller University, investigate how lymphocytes maintain this delicate balance.

A recent paper published in the July, 2007, issue of *Cell* by lead author Elsa Callén, Ph.D., a visiting fellow in Andre Nussenzweig's laboratory, demonstrates that a protein called ATM kinase—which, when mutated, is responsible for the genetic syndrome ataxia telangiectasia (AT)—normally functions to prevent broken DNA strands from joining inappropriately in lymphocytes. ATM kinase also keeps damaged cells from dividing, thus ensuring that genetic stability is maintained. When ATM kinase is absent, cells with broken DNA continue to divide, propagating genetic instability that could lead to cancer.

Considering that hematologic malignancies are found in AT patients, and that ATM kinase is nonfunctional in various cancers, this research holds the promise of helping to unravel the underlying biology of AT and its accompanying blood cancers.