# Chromosome 'glue' surprises scientists

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Proteins called cohesins ensure that newly copied chromosomes bind together, separate correctly during cell division, and are repaired efficiently after DNA damage. Scientists at the Carnegie Institution have found for the first time that cohesins are needed in different concentrations for their different functions.

This discovery helps to explain how certain developmental disorders, such as Cornelia de Lange and Roberts Syndrome arise without affecting cell division essential to development. The research was made possible by a new technique developed by the scientists for membrane-bound cells (called eukaryotes), which enables scientists to gradually reduce the concentration of a protein in living cells. The paper, published on line May 6, and in the May 25, 2010, print edition of Current Biology, opens the door to a better understanding of developmental disorders and to the study of other proteins with multiple functions.

"One of the biggest surprises is that only a small amount of cohesin, the protein 'glue' that keeps replicated chromosomes bound together, is needed for the cell division process and that's what we think cohesin's primary role is," said lead author Jill Heidinger-Pauli at Carnegie's Department of Embryology.

A cell has a four-phase life cycle: growth, synthesis, growth, and mitosis. During the synthesis phase, DNA inside the cell's nucleus is duplicated and two identical daughter chromosomes called sister chromatids result. These twins must remain connected until the cell is ready to divide. This moment occurs in the last step of the cell cycle, the mitosis phase, where

chromosomes condense, and fibrous structures called spindles form. Cohesin keeps the sisters properly glued until it is time for the spindles to pull the sisters to opposite sides of the cell. The cell then separates into two, resulting in two genetically identical cells. Cohesin is also important for other processes outside of cell division. Cohesin plays a critical role in DNA condensation and the repair of DNA damage. Cohesin facilitates efficient DNA repair by gluing sister chromatids together so that if the DNA of one sister is damaged, the other sister can be used as a template for repair. This is critical for preventing the loss of genetic information.

To monitor how much cohesin is needed for these different processes, the researchers exploited a genetic trick which lets a stop codon occasionally code for an amino acid. A codon is a set of three DNA bases that codes either for a particular amino acid or stops the translation (the reading) of the DNA sequence. If the translation process is halted prematurely due to the insertion of a stop codon, a fully functional protein can't be formed. The researchers inserted one or more stop codons early into a DNA sequence that codes for a cohesin protein. Normally this would result in the death of the cell, but the researchers had inserted another mutation, called SUP53, into the cell which resulted in the occasional production of full length cohesin protein. This method resulted in reduced production of cohesin, but did not change the timing of when cohesin was made, or its amino acid sequence.

"We found that DNA repair, chromosome condensation, and the stability of repeat sequences of DNA were all compromised by decreasing cohesion to 30% of normal levels," remarked Heidinger-Pauli. Interestingly, sister-chromatid cohesion and chromosome segregation were not affected even with levels at only 13% of normal. We also looked at how reducing the amount of cohesin changes how it interacts with chromosomes. Normally cohesin binds to regions throughout chromosomes, but we found that when cells only had a small amount of

cohesin, cohesin preferentially binds to the center of chromosomes. We didn't know that this hierarchy existed before, and it helps explain why some cohesin functions might be more affected than others."

Provided by Carnegie Institution