New light shed on cell division

June 14 2011

Genes control everything from eye color to disease susceptibility, and inheritance - the passing of the genes from generation to generation after they have been duplicated - depends on centromeres. Located in the little pinched waist of each chromosome, centromeres control the movements that separate sister chromosomes when cells divide ensuring that each daughter cell inherits a complete copy of each chromosome. It has long been known that centromeres are not formed solely from DNA; rather, centromere proteins (CENPs) facilitate the assembly of a centromere on each chromosome. Understanding how a protein structure can be copied with enough precision to be stable, generation after generation, has been a mystery.

Researchers at the Centre for Chromosome Biology in Galway, Ireland, led by Professor Kevin Sullivan, have visualized these proteins in living cells to analyse how the parts of centromeres assemble themselves as human cells grow and divide. Their new study will be published on 14 June in the online, open access journal PloS Biology.

The Galway group used fluorescent labeling methods to observe the duplication of CENPs on the chromosomes in live cells under the microscope. They also watched how chromosome movement goes awry during cell division when key CENPs were removed from the cell. By comparing how different CENPs are made and then packaged on chromosomes, lead researcher Dr Lisa Prendergast discovered an essential division of labor among the CENPs. A key protein known as CENP-A seems to be specialized for carrying the genetic information of the centromere. Molecular cousins known as CENPs –T and –W

assemble beside CENP-A along the chromosome fiber only after DNA has been replicated. They then go on to do the 'heavy lifting' involved in motoring chromosomes through cell division by producing a structure known as the kinetochore.

It is known that chromosomes inherit more information than is carried in the genes - the field of epigenetics is the study of how a single set of genes can be used to make over 200 different types of cell that make up the body. The centromere is a very special epigenetic element, in which identity itself is carried outside the DNA. This new study provides important experimental and conceptual tools that will help illuminate broader questions about how epigenetics works in normal development and in disease. But because the centromere works at the heart of cell division, it has special relevance in the fight against cancer. Many chemotherapy drugs act by stopping cell division, but their targets also have other roles in the cell, leading to toxic effects in the nervous system and in the rapidly growing cells of hair and skin, for example. "By understanding the inner workings of this molecular machine at a deeper level, we can now think of how to build drugs that target cancer cell division with much greater precision," says Professor Sullivan. "It's important to see how basic research, aimed solely at understanding how life works, can contribute new ideas that support progress in medicine and therapeutics."

By clearly separating genetic inheritance from kinetochore function into different domains on the chromosome fiber, research into cell division and how to stop it in cancer cells can now take place at an accelerated pace.

More information: Prendergast L, van Vuuren C, Kaczmarczyk A, Doering V, Hellwig D, et al. (2011) Premitotic Assembly of Human CENPs -T and -W Switches Centromeric Chromatin to a Mitotic State. PLoS Biol 9(6): e1001082. doi:10.1371/journal.pbio.1001082