Research into chromosome replication reveals details of heredity dynamics

March 3 2011

(PhysOrg.com) -- A novel study from Karolinska Institutet has deepened the understanding of how chromosome replication, one of life's most fundamental processes, works. In a long term perspective these results could eventually lead to novel cancer therapies. The study is presented in the prestigious scientific journal *Nature*.

By studying DNA replication in yeast cells, researchers at Karolinska Institutet have discovered that a protein complex (Smc5/6) helps to release torsional stress created in the DNA molecule when chromosomes are replicated in preparation for a coming cell division.

"Our study also indicates that the stress can propagate more freely along the DNA in a chromosome than was previously thought," says KI professor Camilla Sjögren, head of the team that conducted the study.

The study therefore sheds more light on the mechanisms behind one of life's most fundamental processes. Since topoisomerases, enzymes known to remove replication-related stress in the DNA are common targets for cancer treatments, the finding might eventually lead to new therapies.

When a fertilised egg develops into a complete organism, or when old cells are replaced by new ones, it is done through cell division. If human daughter cells are to survive and develop normally, they must each obtain a full set of 46 chromosomes, which are made of double-stranded DNA helices. Since the original mother cell started as a cell with 46

chromosomes, these must be duplicated before division take place.

During this process, the DNA double helix is separated so that the replication machinery can reach the individual DNA strands. This prising apart of the strands creates stress in the form of over-twisted DNA in the vicinity of the replication zone. If this stress is not removed, replication can be slowed down or even stopped, and this, in turn, can lead to mutagenesis and/or cell death.

"Several modern cancer treatments attack topoisomerases, but there's a problem in that some cancers become resistant to such therapies," says Professor Sjögren. "Now that we've discovered that also the Smc5/6 complex releases the stress which form during the replication process, our results might trigger the development of drugs that target Smc5/6. This could create another tool for inhibiting tumour growth."

More information: Andreas Kegel, Hanna Betts-Lindroos, Takaharu Kanno, Kristian Jeppsson, Lena Ström, Yuki Katou, Takehiko Itoh, Katsuhiko Shirahige & Camilla Sjögren, Chromosome length influences replication-induced topological stress, *Nature*, AOP 2 March 2011, DOI: 10.1038/nature09791

Provided by Karolinska Institutet