New functions for chromatin remodelers

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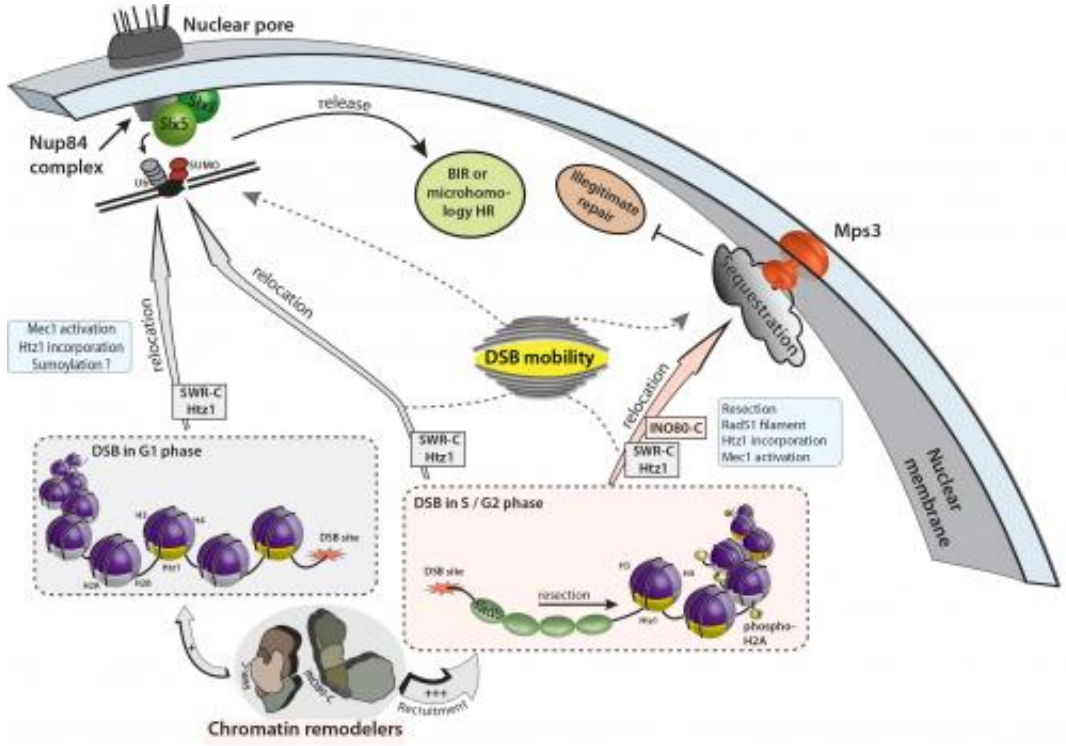

Large molecular motors consisting of up to a dozen different proteins regulate access to the genome, which is essential for the transcription of genes and for the repair of DNA damage. Susan Gasser and her team now reveal a new twist in the activity of such remodelers in the nucleus. In a recent paper in Molecular Cell they show that two related chromatin remodelers help transport broken DNA strands to specific sites in the nucleus for repair. Given the loss of genomic integrity that accompanies

cancer and aging, it is not surprising to find that related remodelers are mutated early in the progression of human cancer.

The architecture of the genome is constantly changing. Depending on the developmental program of the cell, stretches of DNA are compacted and then released again, primarily by modulating the position and composition of histones, the abundant, positively charged proteins that organize DNA into chromatin. The dynamics of DNA accessibility is regulated by a large and diverse group of ATPases, the SWI/SNF family of chromatin remodelers, which shift, replace, and evict histones from chromatin.

Having previously shown a role for a specific chromatin remodeler, the INO80 complex, in the mobility of DNA in the nucleus, the Gasser laboratory has now gone further and explored the significance of DNA long-range movement in the nucleus. They found that the INO80 complex, together with a closely related remodeler called SWR-C (SRCAP in humans), is necessary for the shift of persistent double-strand breaks to sites of repair at the nuclear periphery. Two distinct anchorage sites favor distinct pathways of repair – one involves the processing of proteins bound at the site of damage whilst the other simply sequesters the break from a promiscuous invasion into other regions of the genome. Such invasion often leads to chromosomal translocations, which can generate cancer-promoting fusion proteins. The best-known example of this is a translocation generating the Bcr-Abl tyrosine kinase fusion that drives the development of chronic myelogenous leukemia (CML).

Double-strand break repair is a conserved mechanism that maintains genome integrity in all cells. Double-strand breaks occur during the replication of DNA when particularly difficult sequences (repeats) or RNA polymerases are encountered, or when cells are exposed to ionizing radiation. Unrepaired, such damage can lead to loss of genomic

information and this in turn generates mutations or alleles that compromise control of cell division and/or cell fate. Aging and cancer both threaten patients with compromised DNA double-strand break repair machinery.

The results from the Gasser laboratory now shed light on an important contribution of chromatin remodelers to double-strand break repair. Two of the more common pathways of repair –end joining or the copying of genetic information from an attached sister chromatid – may not require the spatial reorganization of DNA breaks that the Gasser lab has observed. However, key backup mechanisms of break-induced replication or microhomology-mediated recombination seem to require this relocation event. "Up until now many have focused on chromatin remodelers in transcriptional regulation," comments Susan Gasser. "Yet our results point to important roles of these abundant molecular machines in DNA repair. Our work also underscores the importance of nuclear organization for specific repair pathways, something few have thought about at present."

Depending on the phase of the cell cycle, one or both of these chromatin remodelers (SWR-C or the INO80 complex) contributes to the transport of the persistent break, either to a nuclear pore or to a second conserved site on the inner nuclear membrane, where the conserved SUN-domain protein Mps3 suppresses random strand invasion. "Dissecting the different roles of chromatin remodelers and understanding their mode of function goes beyond mere academic interest," comments Gasser. "Many cancers become dependent on chromatin remodelers for survival of the replication damage that accompanies cellular transformation. A better understanding of the processes controlled by these remodelers may help us intervene to kill cancer cells selectively."

More information: Horigome C, Oma Y, Konishi T, Schmid R, Marcomini I, Hauer MH, Dion V, Harata M, Gasser SM (2014) "SWR1

and INO80 chromatin remodelers contribute to DNA double-strand break perinuclear anchorage site choice." *Mol Cell.* 2014 Jul 23. pii: S1097-2765(14)00536-X. DOI: 10.1016/j.molcel.2014.06.027