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An unfolding breast cancer story

BRC1 is one of the most intensely studied proteins in the history of cancer research, and it has more than its fair share of proposed protein partners and postulated activities. Rong Li hopes that he has made sense out of this mountain of information in a paper by Ye et al. starting on page 911. He and his coauthors suggest that BRCA1's effects on transcription and DNA repair have as their root cause a chromatin-unfolding activity of two BRCT repeats at the COOH terminus of the protein.

The assay for unfolding used here has been used with transcriptional activators. It involves targeting BRCA1 or a subset of the protein to multiple (probably several thousand) lacO repeats scattered over 90 Mb of heterochromatin. In 14% of cells expressing BRCA1 linked to the lac repressor there is decondensation of this focused spot of DNA. Either BRCT1 or BRCT2 alone cause an even greater extent of decondensation in a higher percentage of cells (60%), although a construct containing both BRCT repeats has no effect. This suggests that the intact protein may be inhibited for chromatin unfolding, either by the binding of another protein or because of an intramolecular interaction that is relieved by another protein.

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Calcium-coated chromosomes

We know that cations associate with DNA and help to neutralize the negative charges of phosphate groups, but for the most part the analysis of cation effects has not gone any further. Now Strick et al. demonstrate that calcium is distributed on chromosomes in a particular pattern that may implicate it in regulating a chromosomal protein and thus chromosomal structure (page 899).

The author's method of choice is secondary ion mass spectrometry (SIMS). Unlike previous X-ray–based techniques, SIMS yields the depth and localization information characteristic of the results from a confocal microscope. It does so by first using a laser to displace a thin, localized layer of the material under study, and then using mass spectrometry to analyze the displaced material. Strick et al. refine this technique to measure isotopes of a number of cations, but the most interesting results come in the measurements of Mg\(^{2+}\) and Ca\(^{2+}\). Both are associated with mitotic chromatin, but Mg\(^{2+}\) is evenly distributed across the chromatin, whereas Ca\(^{2+}\) is concentrated at the AT-rich axis of each chromosome. This mimics the localization of certain chromosome scaffold proteins, including topoisomerase II (Topo II).

Leading up to mitosis, Topo II is needed to cleave and allow the untangling of DNA as it is condensed. But later in mitosis the activity of Topo II is turned off, perhaps changing the protein into a structural component that helps to keep the center of the condensed chromosome together. The basis of this inhibition was unknown. Now Strick et al. find that the altered ratio of Mg\(^{2+}\) and Ca\(^{2+}\) at the center of the chromosome is, at least in vitro, sufficient to shut off the cleavage activity of Topo II. Mitotic phosphorylation of Topo II may recruit Topo II to the chromosome but, when Ca\(^{2+}\) binds to the chromosomes during mitosis, this local increase in the concentration of Ca\(^{2+}\) may help to shut down Topo II activity. Although this model is appealing, it is yet to be proven, and there may be many other things that the concentrated calcium is doing at the central axis of the chromosome.

Calcium (pseudocolored from blue to orange) localizes to mitotic chromosome axes.

A candidate for that other factor is COBRA1, which Ye et al. isolate as a protein that interacts with BRCT1. COBRA1 by itself can mediate chromosome decondensation. A subset of cancer-causing BRCA1 mutations that result in greater unfolding activity also show greater COBRA1 binding activity, although Ye et al. do not yet know whether such mutations have dominant effects either in cells or people.

Chromatin unfolding could change both transcription and DNA repair by increasing DNA accessibility and helping to recruit other factors. Additional recruitment activities of BRCA1 still seem to be important, as BRCT1 by itself can cause unfolding but not transcription enhancement.