Chromosomal cliques

Are chromosomes distributed randomly within the cell nucleus during interphase, or do they preferentially cluster into specific groups? On page 237, Cornforth et al. address this question, which has been debated vigorously for nearly a century, and conclude that the distribution of chromosomes within the nucleus of human cells is mostly, but not entirely, random. The work provides the most comprehensive analysis to date of chromosome–chromosome spatial associations in human interphase nuclei, and helps to explain why earlier studies sometimes reached conflicting conclusions.

Previous chromosome painting studies using fluorescence in-situ hybridization (FISH) demonstrated that each chromosome generally occupies its own space during interphase, but this did not clarify whether or not particular pairs of chromosomes tended to remain close together. Studies that examined just a few chromosomes at a time sometimes gave seemingly conflicting answers. In the new work, the authors exposed human cells to ionizing radiation to produce chromosome breaks, and used 24-color whole-chromosome painting to examine all possible interchanges between heterologous chromosomes after the breaks rejoined. The frequency of interchanges between two chromosomes should indicate whether or not they were in close proximity.

The large number of chromosomal interchanges in the system strengthened the statistical analysis, enabling the authors to identify very small deviations from spatial randomness. Among all 22 autosomes, most of the deviation from randomness is explained by a single cluster of five chromosomes, with the other chromosomes distributed randomly in the interphase nucleus. The results raise the possibility that this five-chromosome cluster, which has been observed previously, might be functionally significant.

In addition to this cluster, the data show some evidence of other spatial associations that have been suggested by earlier work, but that fail to reach statistical significance in the new work. One possibility is that specific parts of chromosomes might interact without requiring the entire chromosomes to be in close proximity.

Gazing into the gap

Gap junctions are a ubiquitous feature of multicellular life, allowing cells to pass particular classes of biomolecules directly to their neighbors. It is clear that these channels are not just nonspecific pores, but it has been difficult to determine what establishes their specificity. Skerrett et al., whose work appears on page 349, developed a cell perfusion system that allowed them to identify the residues lining an intact gap junction channel. The work helps answer lingering questions about earlier structural models, and identifies some unusual features of gap junctions.

Previous studies determined the basic structure of a gap junction, in which one membrane-spanning α-helix from each subunit of the channel is exposed to the interior of the pore, but this does not reveal what types of residues line the pore or how specificity is determined. The authors generated a panel of mutated connexin proteins, in each case replacing a single amino acid with a cysteine. These altered connexin subunits were expressed in and formed gap junctions between pairs of Xenopus oocytes, and their reactivity with a thiol blocking agent in a novel cell perfusion system pinpointed the residues lining the pore.

The results identify a single α-helix of the connexin as the main pore-lining segment of the gap junction channel, and suggest that a single face of that helix is exposed to the pore. Surprisingly, the apparent pore-lining residues are almost all hydrophobic, an arrangement that is unique among ion channels studied to date.

Skerrett et al. suggest that, unlike classical ion channels, gap junction channels may interact with passing molecules primarily through hydrophobic and weak forces. The new techniques developed for the study also provide a platform for uncovering other structural details about gap junctions. Recently, for example, the authors have used this strategy to map the location of a gate within the pore.