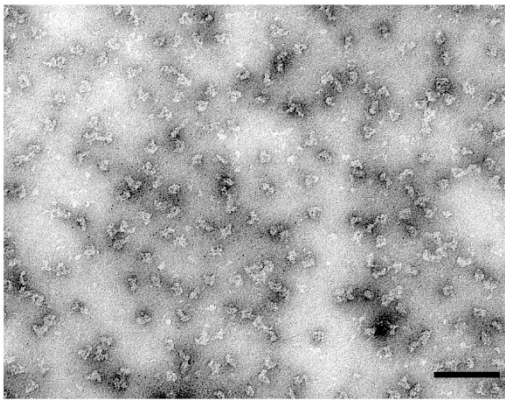
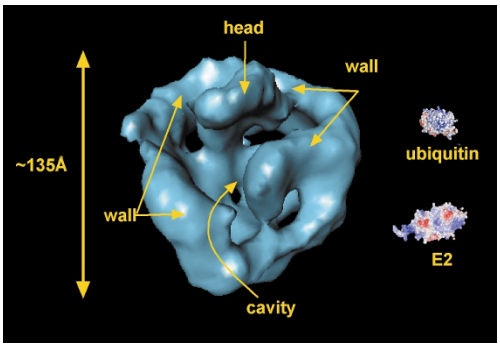
The great divide

When it comes to cell division, bacteria and humans are remarkably alike. Before a cell can divide it has to accurately and completely duplicate its DNA. This is followed by segregation of the replicated DNA molecules that are also known as sister chromatids. Finally, the cell membrane pinches inwardly to produce two daughter cells. Sounds relatively straightforward — but it's not.

Accurate sister chromatid separation during mitosis depends on the intrinsic fidelity of the mitotic machinery and on checkpoints that monitor whether the chromosomes are properly attached to the mitotic spindle. While much is known about the components that make up the cell cycle machinery, how the players in these pathways are regulated and coordinated has been largely unknown. Now, Peters and his colleagues Gieffers and Dube (*Mol. Cell* 7, 907–913; 2001) have solved a low resolution three dimensional structure of the anaphase promoting complex (APC), which controls progression through mitosis.

One important checkpoint control involves the ubiquitin-dependent proteolytic pathway that is one of the major routes by which intracellular proteins are selectively destroyed. This checkpoint operates just before the sister chromatids separate and involves the APC. The APC is composed of 11 core subunits in humans, one of which is a ubiquitin-protein ligase. This protein facilitates the transfer of ubiquitin residues from ubiquitin-conjugating (E2) enzymes to specific substrate proteins. The ubiquitinated proteins are subsequently recognized and degraded by a complex multicatalytic protease called the 26S proteasome. The component of the APC responsible for mediating this reaction can do so in the absence of the other subunits but with a reduced substrate specificity in comparison to the holo-APC. Thus, some of the other APC subunits may regulate the activity of the APC or modulate substrate specificity.





One critical function of the APC is to promote sister chromatid separation. It does this by activating a protease called separase which then cleaves the 'glue' proteins that hold the sister chromatids together. This destruction of the 'glue' proteins allows the sister chromatids to separate.

Analyzing purified APC by negative staining and transmission electron microscopy (top right panels) and cryo-electron microscopy, Peters and coworkers generated a 24 Å model of the APC (bottom left panel). One of the striking features of this model is its asymmetric structure in which the proteins on the outside form a wall around a large inner cavity. Because this cavity could accommodate ubiquitin-charged ubiquitin conjugating (E2) enzymes and known APC substrates, they suggest that this cavity is where the cell cycle-regulated ubiquitination reactions take place, analogous to the inner cavities of the 26S proteasome and chaperone complexes that facilitate protein folding in the cell. This model is an important step in understanding how the APC regulates mitosis and how it helps protect the cell against genomic instability that could otherwise drive it toward cancer.

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