mislocalization of NuMA, because impaired mitotic spindle formation and positioning can compromise chromosome alignment and trigger the spindle assembly checkpoint, similar to observations made for the Golgi (*5*). Alternatively, the lack of PEX11b may lead to an altered peroxisome distribution that is directly sensed by some form of organelle segregation checkpoint or position-sensing machinery. To begin to resolve these questions, Asare *et al.* used optogenetics to experimentally redirect peroxisomes to different regions of the mitotic spindle. Thus, blue light triggered the association of peroxisomes with different microtubule-binding proteins. Remarkably, a mitotic delay was observed only when peroxisomes were directed away from spindle poles to plus ends of microtubules at the spindle midzone, suggesting that peroxisome localization is indeed monitored by the cell. By contrast, targeting peroxisomes to microtubule minus ends at the spindle poles supported normal mitotic progression. These results provide good evidence for the existence of an organelle position-sensing machinery linked to peroxisomes by PEX11b.

The findings of Asare *et al.* support the idea that organelle inheritance, mitotic spindle organization, and cell differentiation are mechanistically coupled. Although many details need to be elucidated, a common theme relating to different organelles is beginning to emerge from this and previous work. This points to the protein kinase Aurora A, which is mutated in several cancers. During spindle orientation, NuMA is a phosphorylation target of Aurora A (*6*) and Aurora A activity is also linked to Golgi inheritance sensing (*7*–*9*). Furthermore, Aurora A activity is spatially restricted to the poles of the mitotic spindle (*10*), possibly providing a simple way to determine where an organelle is relative to different parts of the mitotic spindle (see the figure). Further analysis of the mechanisms of organelle inheritance in multicellular organisms will fill in the details of the basic cellular pathways needed for cell growth and division but may also deliver surprising insights into pathways altered in cancer. ■

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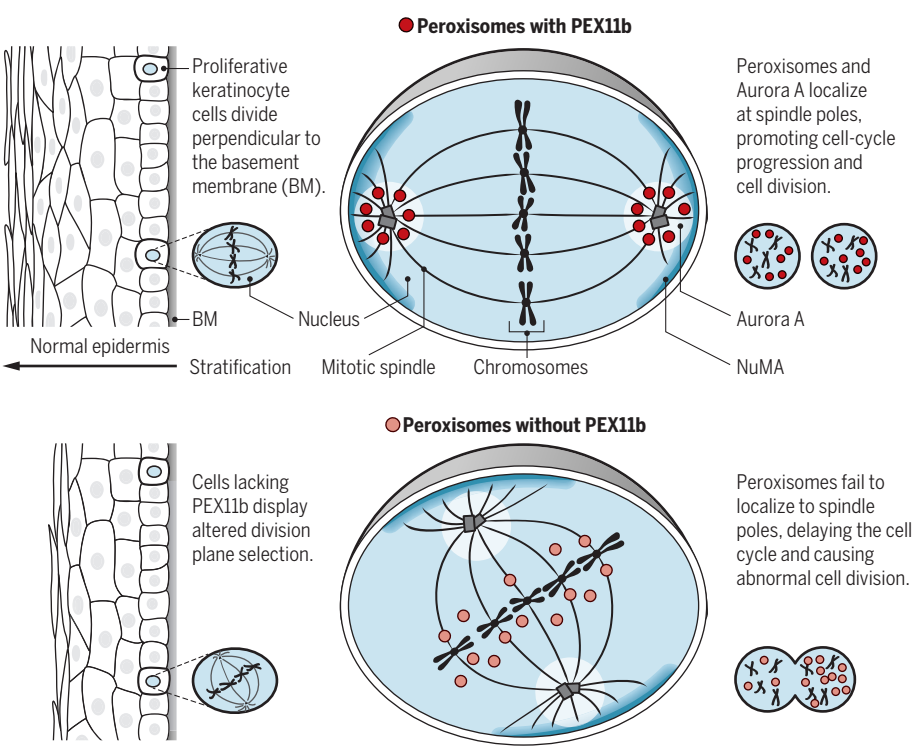
Peroxisome partitioning

In the mammalian epidermis, PEX11b is required for proper orientation of the mitotic spindle and cell division of proliferating keratinocytes.



GRAPHIC: K. SUTLIFF/*SCIENCE*

MOLECULAR BIOLOGY

Chromosome stitch-up?

Ring-shaped protein machines called SMCs act as molecular zips on bacterial chromosomes

By **David J. Sherratt**

Structural maintenance of chromosomes (SMC) complexes are ring-shaped protein machines that have ubiquitous, ancient, and important roles in chromosome management (*1*, *2*). In *Bacillus subtilis*, *Escherichia coli*, and probably most bacteria, functional SMC complexes ensure proper chromosome segregation (*3*–*8*). However, the molecular mechanisms underlying SMC action have remained elusive. On page 524 of this issue, Wang *et al.* elucidate these mechanisms by showing that SMC complexes direct a rapid and progressive "zip-up" of the *B. subtilis* chromosome arms (*9*).

For their study, the authors adapted techniques that interrogate the positional occupancy of proteins bound to chromosomes (chromatin immunoprecipitation–sequencing, or ChIP-seq) and that examine the three-dimensional (3D) conformation of chromosomes (chromosome conformation capture, or Hi-C). These ensemble techniques have been used previously to analyze where and when SMC complexes associate with chromosomes in cells, and what the consequences of these interactions are (*2*, *4*, *6*, *7*). However, these assays typically examine large numbers of heterogeneous cells that contain SMC complexes at different positions on chromosomes, which themselves have differing 3D conformations. Therefore, the assays reveal only an average snapshot of ongoing dynamic processes, leading to loss of biologically relevant information. Furthermore, lack of internal controls prevents assessment of aberrant noise arising, for example, from differential reactivities of DNA segments.

To minimize these limitations, Wang *et al.* initiated synchronous loading of SMC complexes onto chromosomes. They then tracked SMC action every few minutes, using ChIP-seq to assess SMC positioning and Hi-C to assess chromosome architecture.

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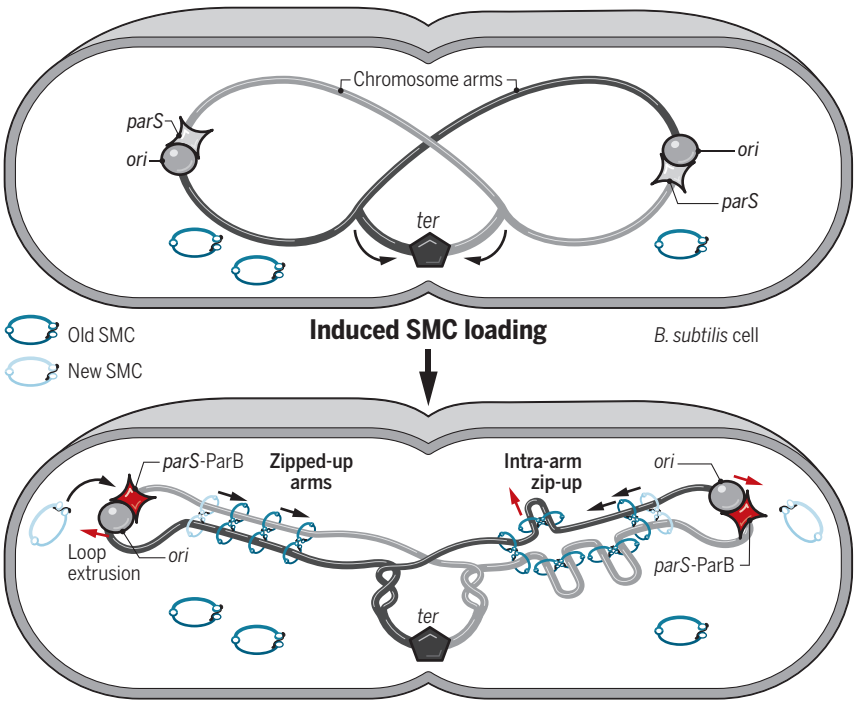
Chromosome zip-up

SMC complexes facilitate *B. subtilis* chromosome segregation by zipping up the arms of a circular chromosome.



To achieve synchronous loading, the authors constructed cells with a single *parS* site close to the chromosome replication origin (*ori*) (see the figure). Protein ParB binds to *parS* sites, and previous work has shown that SMC complexes load preferentially at ParB-bound *parS* (*6, 7*). Induction of ParB synthesis in cells initially lacking ParB led to synchronous loading of SMC complexes at *parS* and their subsequent bidirectional movement along DNA away from *parS*, thereby zipping up and aligning the left and right arms of the circular chromosome all the way to the replication terminus (*ter*) more than 2 million base pairs (bp) away (see the figure). The authors also used cells that had *parS* located at other chromosome positions to investigate the relationship between replication and SMC loading position. In these cases, chromosome segments on either side of *parS* were zipped up.

The population zip-up rate was ~800 bp/s, independent of where *parS* was located. This is more than 10 times as fast as the transcription rate, but similar to the replication speed. Yet, the zip-up rate was apparently replication independent, because it was not influenced by where SMC loading occurred relative to replication initiation and direction. Newly synthesized SMC complexes are always enriched at *parS;* the authors conclude that zip-up is directed by continuous loading of SMC complexes at *parS* and their movement away, rather than by sequential adding of new SMC complexes at the zip's leading edge.

Wang *et al.* argue that at least two associated SMC ring complexes act together during the zip-up, because the rates of travel along the two chromosome arms were not identical. In particular, converging transcription reduced the rate of zip-up on one arm without influencing that on the other arm. Nevertheless, the authors infer coordinated action of pairs of SMC rings in cells in which *parS* had been moved away from *ori* toward *ter*. In this case, once chromosome-associated SMC complexes on one side of *parS* reached *ter*, both they and the *ter*-distant complexes on the other side of *parS* dissociated, as judged by zip-up cessation.

A zip-up process like that proposed by Wang *et al.* generates a DNA loop in its wake. This loop is extended as an SMC complex progresses along the chromosome. In cells, this progress may lead to movement of the SMC complexes with respect to a static chromosome, or to movement of the DNA with respect to relatively static SMC complexes, which themselves may be clustered (*4, 6, 8*). In the latter case, this would facilitate cellular chromosome movement and segregation. In eukaryotic cells, loop extrusion has been implicated in the formation of topologically associating domains, in facilitating sister chromosome segregation, and in mitotic chromosome condensation-organization (*1, 10*).

Although these experiments are impressive, they do not reveal the number of SMC rings acting on a chromosome at any one time and the positional relationship between them. The suggestion that at least two associated SMC rings act together is consistent with the demonstration that in live *E. coli*, two SMC dimers are the minimum functional unit (*8*). It remains to be shown whether the zip-up speed relates directly to the rate of SMC complex travel; nevertheless, the rate scales linearly with time, indicating an energy-driven process rather than a random walk.

If the ~800 bp/s zip-up does reflect SMC complex translocation, what is the mechanism? SMC complexes entrap DNA within the protein rings in reactions requiring adenosine 5′-triphosphate (ATP) binding and hydrolysis (*2–4, 11*). Nevertheless, they have low ATPase activities in the test tube and load/unload onto DNA slowly in cells (*2, 4, 8*). Therefore, it is unlikely that they move by tracking along the DNA helix like ring DNA translocases, which exhibit high ATPase activity as they translocate rapidly (*12*). Badrinarayanan *et al.* have proposed a "rock climber" model to account for these data and the fact that any SMC translocation along chromosomes has to negotiate transcription-translation-replication, as well as tightly bound proteins (*8*). In this model, substantial segments of DNA are translocated in single ATP hydrolysis–driven steps by alternate DNA binding and unbinding to two connected SMC rings, or indeed between the hinge and head of a single ring. Therefore, rather than DNA sliding freely within a ring, discrete DNA-bound SMC complexes may have key roles in the translocation mechanism by directing the regulated entry and exit of one or more DNA segments.

The experiments reported by Wang *et al.* may help to explain the behavior of other SMC complexes. Preferred loading sites and bidirectional movement away from those sites have been inferred for eukaryotic SMC complexes, consistent with conserved architectures and DNA entrapment within the SMC ring (*2*). Answers to some of the outstanding issues may emerge once single-molecule in vitro experiments, which avoid ensemble averaging, fully recapitulate the in vivo behavior of SMC complex action. ■

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