genes, the evolution of pleiotropy, the accumulation of modifier mutations, and so on. The authors themselves brand the chapter "conceptual meanderings." But it is one thing to meander, another to synthesize. This lack of coherence lends the book a diffuse, unrigorous quality and is, in the end, its most serious problem. Now and then the clash of ideas gets so bad that the text slips into unintelligibility, as when we are told, "The innate complexity of genetic systems necessarily leads to emergent properties arising from epigenetic processes that integrate the output components of myriad local genetic programs into a functional global phenotype." Such talk seems an unlikely first step to clearer understanding.

Phenotypic Evolution is representative of a popular trend—some pet theory (take your pick: plasticity, development, complexity theory, or chaos) gets elevated to its rightful place as "the" way to think about evolution. But this longing to dress up biology in unusual new perspectives has, so far, yielded more book deals than results. Although new ways of thinking will surely be required in the attempt to unravel the genetical evolution of the phenotype, considerable care and taste are needed in their selection. Schlichting and Pigliucci's confused admixture is not the perspective we have been waiting for.

NOTA BENE: CD-ROMS

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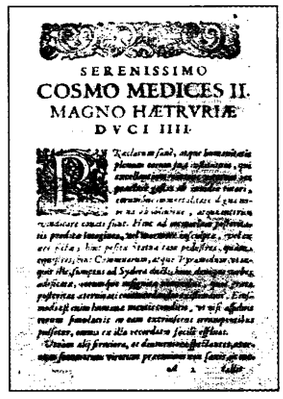
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Galileo Galilei's *Sidereus Nuncius* (1610) has been called the most earthshaking book published in the history of astronomy. In this work, Galileo defined a modern view of the universe and our place in it. His most important observation—that Jupiter was at the center of what appeared to be a mini–planetary system—simultaneously demonstrated that the sun and humankind were not foci of the heavens. Benjamin Franklin's *Experiments and Observations on Electricity* (1751) is one of the most important treatises of the 18th century because of its systematic approach to a physical phenomenon. The rarity and fragility of these original documents have for centuries put them out of reach for all but a very select, privileged few. Thanks to digitizing technology and Adobe's Acrobat Reader, however, we now can scroll page-by-page through carefully scanned original versions of these fascinating works. Other significant historic scientific books also available on CD-ROMs (and as downloadable Acrobat files) from Octavo Corporation (Oakland, CA; www.octavo.com) include Nicholas Copernicus' *De Revolutionibus Orbium Coelestium* (1543), Robert Hooke's *Micrographia* (1664), William Harvey's *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* (1628), and Isaac Newton's *Opticks* (1704).

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PERSPECTIVES: CELL CYCLE

The Difficulty in Separating Sisters

Terry L. Orr-Weaver

One of the defining events during cell division (mitosis) is the separation of sister chromatids that are attached to each other and to the mitotic spindle, a process called cohesion release. But we are only now beginning to understand how the powerful cohesive forces that hold the sister chromatids together are overcome. In the budding yeast, *Saccharomyces cerevisiae*, the chief player seems to be the Esp1 protein—a so-called separin—which is also found in human cells, raising the possibility that the mechanism of cohesion release is highly conserved (*1*). On page 418 of this issue, Zou *et al.* add another piece to the puzzle with their report that an oncogene, *PTTG* (pituitary tumor-transforming gene), acts as a regulator of Esp1. This suggests that defective regulation of cohesion may contribute to cancer by promoting chromosome instability (*2*). Like a classic murder mystery plot, the prime suspect for "doing in" sister-chromatid cohesion, the anaphase-promoting complex (APC), now turns out to be a mere accomplice, with the less colorful Esp1 character actually responsible for the deed.

Physical association of the sister chromatids is crucial for their stable attachment to microtubules from opposite spindle poles and for their proper segregation at the transition from metaphase to anaphase. Cohesin, a conserved multiprotein complex, is essential for the tight association of the sister chromatids, which is established as the DNA is replicated during S phase (*3*). The cohesin complex is localized along the length of the sister chromatids and, as shown by a report in last week's *Science*, is also bound to the centromere (the constricted area of the chromosome to which spindle microtubules bind) (*4*). In budding yeast, two cohesin subunits, Scc1p (also called Mcd1p) and Scc3p, dissociate from the chromatids at the onset of anaphase, coinciding with release of cohesion.

Ubiquitin-mediated proteolysis is necessary to activate the transition from metaphase to anaphase. The APC tags mitotic cyclins with a ubiquitin marker, targeting them for degradation; the cells are then able to exit mitosis. The APC also has other substrates that must be degraded to ensure sister-chromatid separation (*5*). The initial theory that the APC directly releases cohesion by degrading cohesin was disproved by the finding that cohesin subunits persisted into telophase, the final step of cell division (*6, 7*). Rather, it turned out that APC triggers the degradation of a group of proteins called securins that inhibit sister-chromatid separation. Securins include Pds1p in *S. cerevisiae* and a different protein, encoded by the *cut2*

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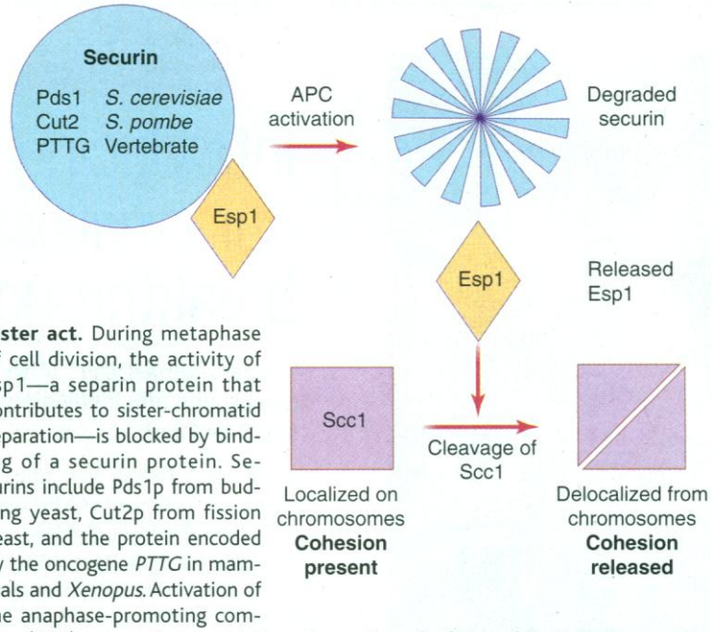
gene, in the fission yeast *Saccharomyces pombe* (*8, 9*). Zou *et al.* (*2*), screening for APC substrates in *Xenopus*, have now identified a third securin, PTTG. These investigators have shown that addition of a nondegradable form of PTTG to extracts from *Xenopus* eggs (in which nuclear division occurs) prevented the separation of sister chromatids but did not block exit from mitosis, firmly placing this protein in the securin family.

Although APC-targeted proteolysis does away with inhibitors of chromatid separation, a recent surprise from *S. cerevisiae* is that dissociation of cohesin from the chromatids, with the resulting release of the sisters, is triggered by another proteolysis event: cleavage of the Scc1p cohesin subunit. According to Uhlmann *et al.* reporting in a recent issue of *Nature* (*1*), this cleavage is dependent on the separin Esp1p. The investigators observed dissociation of Scc1p from chromatin treated with extracts of wild-type yeast cells but not with extracts of *esp1* mutants. Furthermore, the dissociation of Scc1p is accompanied by its cleavage at two sites. Esp1p-dependent cleavage and delocalization of Scc1p was confirmed in vivo, and mutation of both of the cleavage sites resulted in failure of sister separation and persistent chromosomal association of cohesin. It is not known whether Esp1p is the Scc1p protease or merely activates a protease that cleaves Scc1p. The carboxyl terminus of Esp1p is conserved, with orthologs present in vertebrates, but it remains to be determined whether the homologs of Scc1p are cleaved in *S. pombe* or multicellular organisms. Nevertheless, the implications of a conserved regulatory mechanism are clear.

Thus, it seems likely that the securins hold the sister chromatids together by inhibiting Esp1p's ability to cleave and delocalize cohesin. The role of Esp1p in sister separation was recognized initially because of its localization in a complex with the securin Pds1p (*10*). Zou *et al.* also recovered the PTTG protein through its ability to coimmunoprecipitate with human Esp1, in addition to their identification of PTTG as an APC substrate and a securin. Although Pds1, Cut2, and PTTG all bind to their Esp1 homologs, the three sets of proteins are not homologous. Thus, they may regulate Esp1 through entirely different mechanisms, and even within one organism there may be several Esp1 regulatory pathways that are functionally redundant. For example, under normal growth conditions, yeast strains that are deficient in *pds1* do not have premature sister-chromatid separation, indicating that other routes for inhibition of Esp1 exist.



Sister act. During metaphase of cell division, the activity of Esp1—a separin protein that contributes to sister-chromatid separation—is blocked by binding of a securin protein. Securins include Pds1p from budding yeast, Cut2p from fission yeast, and the protein encoded by the oncogene *PTTG* in mammals and *Xenopus*. Activation of the anaphase-promoting complex (APC) causes the degradation of securin and release of Esp1. Esp1 promotes the cleavage of the Scc1 subunit from the cohesin multiprotein complex, which holds the sister chromatids together. Cleavage of Scc1 results in release of cohesion between the sister chromatids, and their separation to opposite spindle poles.

In multicellular organisms the cleavage and release of cohesin is more complex. Although cohesins remain on the chromosomes until anaphase in budding yeast, they dissociate at prophase in *Xenopus* extracts, implying that other proteins maintain cohesion until anaphase in higher eukaryotes (*11*). It is possible that even if most of the cohesin complexes dissociate from the chromosomes in prophase, an undetectable but critical residual fraction remains attached to the chromosomes until anaphase. Thus, there are still a number of questions about the function of Esp1 that remain to be answered. Is Esp1 involved in cohesin delocalization in prophase, and does this involve the proteolysis of Scc1? If Esp1 acts at prophase in higher eukaryotes, how does it escape inhibition by securins before the APC is activated? Is residual Scc1 cleaved in an Esp1-dependent process that is downstream of APC?

Many transformed cells show chromosome instability that results in aneuploidy (an odd number of chromosomes), suggesting that defects in mitotic chromosome segregation could be the root cause of some cancers (*12*). Certain colorectal tumor cell lines with chromosome instability carry mutations in a gene called *BUB1* (*13*). The Bub1 protein participates in a spindle assembly checkpoint that can delay anaphase by blocking the activation of APC. Regulation of sister-chromatid cohesion and separation is essential for ensuring the proper segregation of chromosomes. Thus, defects in cohesion could lead to chromosome instability and cancer. The properties of the human securin PTTG are at least consistent with this hypothesis (*14, 15*). PTTG was identified on the basis of its high levels of expression in pituitary tumors. Overexpression of PTTG impedes cell division, consistent with its role in blocking sister separation. This may then lead to segregation errors and aneuploidy. The PTTG protein does have the properties of an oncogene in that if it is overexpressed in transformed fibroblasts the cells do not show growth inhibition in soft agar, and they form tumors when injected into nude mice.

Although Esp1 emerges as the perpetrator of cohesin's demise, loose ends and mysteries remain. For example, it has not yet been determined whether cleavage of Scc1 occurs in higher eukaryotes and, if it does, during which stage of mitosis. It will be interesting to find out whether Esp1 is a new protease. The regulation of Esp1 by the securins needs to be sorted out, and is likely to be a complex pathway, because different securins may use distinct mechanisms to regulate Esp1. Furthermore, there is the intriguing possibility that understanding the securins and Esp1 will provide us with new approaches to treating cancer.

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