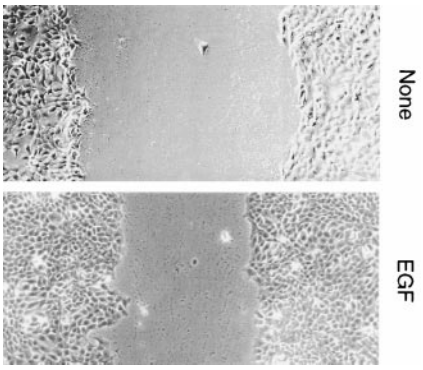
Knowing When to Stop

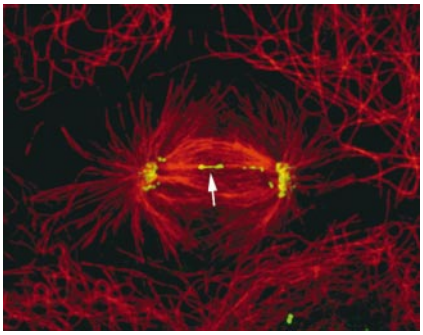
On page 465, Hintermann et al. suggest a way in which keratinocytes may balance the competing forces of adhesion and locomotion. They show that an integrin primarily associated with adhesion ($\alpha_6\beta_4$) can inhibit the signaling cascade downstream of an integrin associated with migration ($\alpha_3\beta_1$). This trans-dominant inhibition between two integrins that recognize laminin-5 (Ln-5) may tell wound-healing keratinocytes when they need to stop migrating and settle down.



The early stages of wound healing are dominated by chemotactic signals that lure keratinocytes into closing large gaps. At this stage, $\alpha_3\beta_1$ dominates and, according to Hintermann et al., engagement of $\alpha_6\beta_4$ does not inhibit this chemotactic motility. But later on, as extracellular matrix and basement membrane are re-established, the fine tuning of cell position may rely more on haptotaxis—cell migration triggered by adhesion receptors. Hintermann et al. suggest that this is where $\alpha_6\beta_4$ may come back into play. They find that $\alpha_6\beta_4$ engagement can inhibit $\alpha_3\beta_1$-mediated haptotaxis. This occurs not by a change in adhesion, but by $\alpha_6\beta_4$'s recruitment of the erbB-2 receptor and activation of phosphoinositide 3-kinase (PI3-K). Further contact between $\alpha_6\beta_4$ and Ln-5 is expected to result in strengthened cell anchoring, but the earlier signaling event may ensure that migration and anchoring are never at cross purposes.

Stretching Out Kinetochores

Kinetochores in prometaphase must satisfy opposing requirements: they must be big enough to ensure capture of at least some microtubules, but small enough such that capture of microtubules from both spindle poles (resulting in a merotelic orientation) is unlikely. On page 517, Cimini et al. report that, at least in PtK1 cells, this trade off often goes wrong. The resulting merotelic orientations are a major source of aneuploidy.

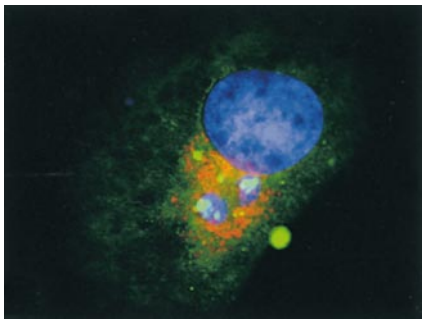


Cimini et al. detected lagging merotelic chromosomes in 20/1,631 (1.16%) normal mitoses, and 135/758 (17.55%) mitoses after a block with the spindle-depolymerizing drug nocodazole. Microtubules from the two spindle poles were attached at either end of the kinetochores of these lagging chromosomes, resulting in stretched kinetochores. Merotelic chromosomes can be detected in metaphase, and it seems that the merotelic orientation arises when the chromosome is in a normal paired configuration, with chromosome disjunction then resulting in a single merotelic chromatid being left at the spindle equator.

The authors do not yet know if imposing a longer delay in metaphase would lead to correction of this problem. But they do know that cells probably do not turn on such a delaying mechanism themselves, as merotelic chromosomes do not stain for the checkpoint markers Mad2 or 3F3/2. This is not surprising. Merotelic attachment should mimic the opposing forces of a normal bipolar attachment, and thus escape detection by the spindle checkpoint.

Aggresoming Viruses

Misfolded proteins are actively concentrated into structures called aggresomes. On page 449, Heath et al. suggest that certain large cytoplasmic DNA viruses have co-opted this cellular machinery to form viral factories. These cytoplasmic subdomains contain high concentrations of viral subunits and thus facilitate viral replication.

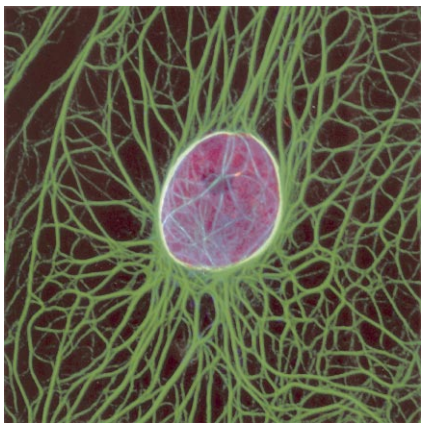


Heath et al. show that both aggresomes and viral factories are surrounded by a vimentin cage and both form near the cell's microtubule organizing center (MTOC). Microtubules are required for both the establishment and maintenance of the two structures. Viral nucleoprotein cores are similar in size to the balls of unfolded proteins that are collected by the aggresome-forming machinery, although the virus must also have a mechanism for breaking apart its vimentin cage so that completed viral particles can be released. Heath et al. are now interested in identifying phosphorylation sites on vimentin that may control this cycle of assembly and disassembly.

Intermediate Filaments on the Move

Intermediate filaments (IFs) such as vimentin and keratin provide structural support for cells so the cells can withstand physical stress. They have been thought of as static structures,

but recent work with green fluorescent protein fusion proteins has uncovered evidence that IFs move. Now Yoon et al. provide the first detailed analysis of movements of individual keratin tonofibrils (page 503).

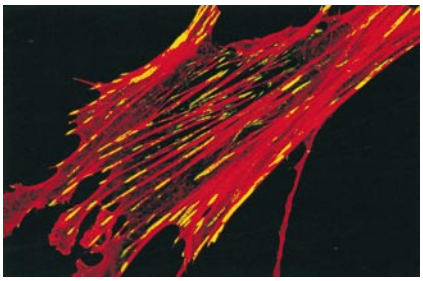


Keratin tonofibrils move ~15-fold slower than vimentin filaments, and parallel tonofibrils only 0.3–1-μm apart can move in opposite directions. In nocodazole, these movements are no longer measurable, but bending and wave-like propagation are still apparent. The wave propagation (though not the bending) are eliminated by addition of a phosphatase inhibitor, suggesting that phosphorylation changes mediate the wave movements. Yoon et al. are now identifying the relevant phosphorylation sites so that they can test whether the wave movements help transmit signals about cellular tension from the cell surface to the nucleus.

Sustained Tension

Calcium-dependent phosphorylation of myosin light chain (MLC) by myosin light chain kinase (MLCK) favors myosin-based contraction. On page 569, Katoh et al. propose that this mechanism is used for rapid, short-lived contractions, whereas RhoA and its target Rho kinase regulate sustained contractions necessary for maintaining cellular tension and stress fibers.

In previous work, Katoh et al. established an in vitro system in which stress fibers undergo contractions that are calcium and MLCK dependent. In the new work, they use glycerol rather than Triton X-100 for a second extraction and thus derive stress fibers that retain RhoA and Rho kinase, and that can therefore undergo calcium-independent contractions regulated by these two proteins. As has been observed previously, interfering with RhoA in living cells dissolves stress fibers, probably because of the loss of tension. Katoh et al. now hope to use the in vitro system to measure force production by individual stress fibers, and to test whether contraction in nonmuscle cells occurs via the sort of thin-filament sliding seen in muscle cells.



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