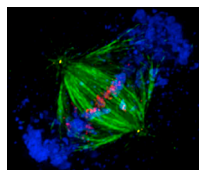


A MUG shot of spindle assembly



In cells undergoing MUG, the mitotic spindle (green) is assembled, despite the separation of centromeres and kinetochores (red) from the bulk of chromosomal DNA (blue).

Kinetochores can organize the mitotic spindle without assistance from chromosome arms or centrosomes, report [O'Connell et al.](#)

Several pathways contribute to assembly of the microtubule-based mitotic machinery that segregates chromosomes. Microtubules grow from centrosomes and capture chromosomes by attaching to kinetochore complexes at their centromeres. Microtubules originating near the chromosomes are also involved, and can even form a spindle in the complete absence of centrosomes. The integration of these pathways is thought to rely on a gradient of RanGTP, a small GTPase activated by a nucleotide exchange factor present on chromatin that liberates microtubule nucleation and stabilization factors in the vicinity of chromosomes.

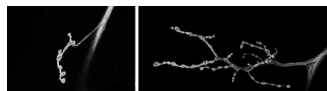
O'Connell et al. were thus puzzled by the organization of

spindles in HeLa cells undergoing mitosis with unreplicated genomes (MUG), a situation in which kinetochores and centromeric DNA are separated from all other chromatin. This unusual event—induced by prolonged treatment with hydroxyurea—results in the formation of a robust spindle prominently centered on kinetochores, while the bulk of the chromatin is pushed out to the cell periphery. This sidelined chromatin still produced high levels of RanGTP but the kinetochores of MUG cells lay outside this region, indicating that they need not reside within the gradient peak to organize and attach to spindle microtubules. Knocking down a key kinetochore protein called Nuf2 did prevent spindle assembly, highlighting the importance of kinetochores in this process.

This suggests that kinetochores are the dominant factor in building mitotic spindles. Human cells undergoing MUG provide a unique system to reveal spatial cues that direct microtubule growth *in vivo*, says author Chris O'Connell. Previously, these experiments could only be conducted *in vitro*, such as assays with egg extracts.

O'Connell, C.B., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200903076.

Autophagy balances a Highwire act in synapse development



NMJs are smaller in flies lacking Atg1 (left) and overgrown in flies overexpressing the protein (right).

Autophagy plays a surprisingly constructive role in *Drosophila* synapse development, counteracting a proteasome-mediated degradation pathway, say [Shen and Ganetzky.](#)

The E3 ubiquitin ligase Highwire (Hiw) limits neuromuscular junction (NMJ) growth presumably by sending proteins to their destruction at the hands of the proteasome. Shen and Ganetzky wondered whether protein degradation by autophagosomes might similarly regulate NMJ development.

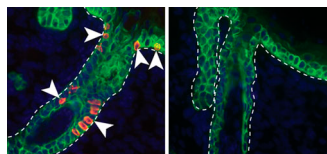
Flies with impaired autophagy had smaller NMJs than wild-type flies, whereas overexpressing an inducer of autophagy called Atg1 caused NMJ overgrowth. Activating autophagy by feeding larvae with rapamycin also enlarged NMJs, indicating that the degradative pathway promotes rather

than inhibits synaptic development. The supersized NMJs of flies overexpressing Atg1 were remarkably similar to those of *hiw* mutants, leading the authors to investigate whether the two pathways were linked. Hiw protein levels were reduced upon autophagy induction, while boosting levels of the ubiquitin ligase reversed the NMJ overgrowth induced by Atg1. Autophagy therefore promotes synaptogenesis by degrading Hiw and blocking its inhibitory effects.

Although it is usually thought of as a nonspecific catchall for protein destruction, there are a few examples where autophagy is more discriminating in its function. The authors therefore want to determine whether Hiw is specifically targeted for destruction by autophagosomes and, if so, how the process occurs. They point out that autophagy is ideally suited to regulating synaptic growth and remodeling because the pathway responds to a wide range of environmental cues.

Shen, W., and B. Ganetzky. 2009. *J. Cell Biol.* doi:10.1083/jcb.200907109.

Merkel cells bear the touch of epidermis



Merkel cells (red) fail to differentiate from epidermal stem cells in mouse skin lacking Atoh1 (right).

Van Keymeulen et al. resolve a 130-year-old mystery over the developmental origin of specialized skin cells involved in touch sensation.

First described in 1875, Merkel cells are neuroendocrine cells that reside in the vertebrate epidermis, passing mechanical stimuli on to sensory neurons. In mice, they are mainly found in the paws and around the whiskers but, because they express proteins characteristic of both epithelial and neuronal cells, scientists have long debated whether Merkel cells develop from the epidermis or neural crest.

Van Keymeulen et al. traced the lineage of Merkel cells by fluorescently labeling cells derived from either epidermal or neural crest progenitors. This revealed that Merkel cells originally emerge from the embryonic epidermis. In addition, epidermal stem cells in adult mouse skin replenish the Merkel cell population as they slowly die off over time. The researchers also found that a transcription factor called Atoh1 is required for epidermal progenitors to differentiate into Merkel cells—mice lacking Atoh1 in their skin failed to develop any of the mechanotransducing cells.

Atoh1 acts as a tumor suppressor to prevent an aggressive skin cancer called Merkel cell carcinoma, says senior author Cédric Blanpain. His team now wants to investigate the precise function of the transcription factor in Merkel cell differentiation, as well as the signaling pathways that regulate the process.

Van Keymeulen, A., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200907080.