In This Issue

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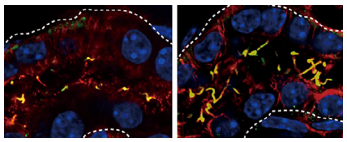
Ndel1 keeps cilia retracted



Compared with wild-type (left), the kidneys of *NDEL1* hypomorphic mice contain more quiescent cells sporting a primary cilium (yellow).

The dynein accessory factor Ndel1 stops proliferating cells from regrowing a primary cilium, Inaba et al. reveal.

When quiescent cells reenter the cell cycle, they retract their primary cilium so that the ciliary basal body can be used as a centriole to form one of the two centrosomes that organize the mitotic spindle. A centriolar protein called trichoplein prevents proliferating cells from reassembling a cilium by binding and activating the kinase Aurora A. When cells return to quiescence, the E3 ubiquitin ligase $CRL3^{KCTD17}$ targets trichoplein for degradation, allowing cilium regeneration.

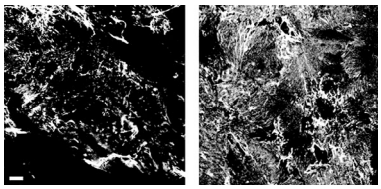
The dynein accessory factor Ndel1 contains a domain similar to trichoplein and localizes to the mother centriole/basal body. Inaba et al. found that knocking down Ndel1 caused proliferating cells to prematurely degrade trichoplein, resulting in cilium regrowth and cell cycle arrest. This effect was reversed by overexpressing trichoplein or knocking down the ubiquitin ligase subunit KCTD17.

Serum-starved cells transiently down-regulated Ndel1 as they reentered quiescence. Overexpressing Ndel1 prevented these cells from degrading trichoplein and regenerating a cilium. Ndel1 therefore suppresses ciliogenesis and cell cycle exit by stabilizing trichoplein. Accordingly, the kidney epithelia of *NDEL1* hypomorphic mice showed an increased number of ciliated, quiescent cells.

Senior author Masaki Inagaki now wants to further explore the relationship between cilia and cell cycle regulation. He points out that, as well as regulating centriole availability, primary cilia act as signaling hubs for numerous growth factors and could therefore have a key role in suppressing tumorigenesis.

Inaba, H., et al. 2016. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201507046

Disrupted desmosomes drive fibrosis



Compared with control cells (left), fibronectin is up-regulated in cardiomyocytes lacking PKP2 (right).

Dubash et al. describe how the loss of desmosomal proteins activates a profibrotic signaling pathway in cardiomyocytes.

Plakophilin-2 (PKP2) is a key structural component of desmosomes, intercellular adhesions that are particularly important for holding cells together in mechanically stressed tissues such as the heart. Accordingly, mutations in *PKP2* disrupt the junctions between neighboring cardiomyocytes and cause arrhythmogenic cardiomyopathy. This disease is also associated with the formation of fibrotic lesions, but how the loss of PKP2 contributes to tissue fibrosis remains unknown.

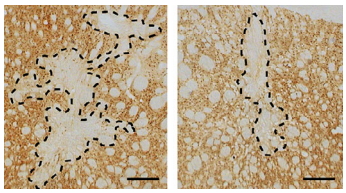
Dubash et al. found that knocking down PKP2 in cultured cardiomyocytes, or removing one copy of the *PKP2* gene from mice, increased expression of the profibrotic growth factor TGF-β1. This, in turn, activated a p38 MAP kinase–dependent signaling pathway that up-regulated multiple inflammatory and extracellular matrix proteins known to promote tissue fibrosis.

PKP2's desmosomal binding partner, Desmoplakin, was destabilized in PKP2's absence, Dubash et al. discovered, and restoring Desmoplakin levels reversed the up-regulation of TGF-β1 and its profibrotic effectors. Knocking down Desmoplakin, in contrast, was sufficient to activate TGF-β1 signaling even in the presence of PKP2.

First author Adi Dubash says that disrupted desmosomes may induce fibrosis in several other human diseases. The next question, he says, is to determine how the loss of Desmoplakin up-regulates TGF-β1 transcription.

Dubash, A.D., et al. 2016. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201507018

Ataxin-3 phosphorylation protects neurons



Expanded ataxin-3 causes an extensive loss of neurons (brown) in rat brains (left). But the amount of neurodegeneration is reduced when serine 12 is mutated to aspartate (right).

Phosphorylation reduces the neurotoxic effects of a protein mutated in Machado-Joseph disease (MJD), Matos et al. reveal.

Ataxin-3 is a ubiquitously expressed deubiquitinase that is proposed to function in a variety of cellular pathways. In MJD (also known as spinocerebellar ataxia type 3), a polyglutamine tract in ataxin-3's C-terminal tail becomes abnormally expanded, causing the protein to aggregate and induce cellular stress. Only certain populations of neurons die in MJD patients, however, suggesting that cell type–specific posttranslational modifications might affect the toxicity of expanded ataxin-3.

Matos et al. found that ataxin-3 is phosphorylated on serine 12 in cultured rat neurons, and mutating this serine to a phosphomimetic aspartate residue inhibited the enzyme's deubiquitinase activity. Expressing an expanded version of ataxin-3 in cultured neurons induced dendritic shrinkage and a loss of both excitatory and inhibitory synapses. This effect was attenuated when serine 12 was mutated to aspartate. In contrast, mutating this serine to a nonphosphorylatable alanine residue caused normal, nonexpanded ataxin-3 to induce dendrite and synapse loss.

Despite these opposing effects on neuronal morphology, mutating serine 12 to either aspartate or alanine reduced the ability of expanded ataxin-3 to aggregate and induce neurodegeneration in rat brains. Senior author Ana Luisa Carvalho says that modulating ataxin-3 phosphorylation could be an effective way to treat MJD patients. To this end, she wants to identify the kinase that phosphorylates serine 12.

Matos, C.A., et al. 2016. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201506025

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