Separating daughter cells by tension release

Cell division culminates in cytokinesis, the step that separates the two daughter cells after successful completion of the previous cell cycle phases. The physical separation by severing the bridge that connects the cells, termed abscission, involves the endosomal sorting complex required for transport-III (ESCRT-III). Piel and colleagues now report that ESCRT-III assembly and abscission are triggered by releasing the tension that the daughter cells exert on the intercellular bridge (*Science* **339,** 1625–1629; 2013).

The authors seeded cells on different sizes of disc-shaped fibronectin micropatterns and observed that abscission was delayed when cells were subjected to a low degree of spatial confinement and were able to move apart from each other. Surprisingly, the longer abscission time was the result of increased pulling forces on the bridge, which in turn depended on ROCK-regulated cell contractility and high membrane tension. The authors performed a series of laser ablation experiments combined with RNAi-mediated depletion of known regulators of abscission, including the CHMP4B ESCRT-III component. These results showed that reducing tension by laser-mediated cutting of the bridge on one side induced the late-stage assembly of the ESCRT-III complex and subsequent abscission of the remaining part of the bridge. Although the mechanism by which tension release promotes ESCRT-III complex formation remains to be elucidated, these findings add to our understanding of how the timing of cytokinetic abscission is regulated. AIZ

A multiple myeloma survival factor

Multiple myeloma is a genomic and phenotypic heterogeneous disease, and thus challenging to treat. Discoveries of non-oncogenic addiction factors, that is, genes that are not affected by mutations and required for all myelomas to survive, would be highly beneficial for identifying new therapeutical targets.

Using an unbiased RNA interference screen, Staudt and colleagues (*Cancer Cell* http://doi.org/k69; 2013) identified caspase-10 as a non-oncogenic addiction target in myeloma, but not in lymphoma, lines. Myeloma viability was found to be dependent on catalytically active caspase-10. The master transcription factor IRF4, which is essential for survival of myeloma, was shown to upregulate both capase-10 and the large isoform of caspase-like protein ($cFLIP_L$) in myeloma cells; furthermore, $cFLIP_L$ interacted with caspase-10 to increase its activity. Interestingly, inhibition of caspase-10 did not affect apoptosis, but instead increased autophagic flux. BCL-2-associated transcription factor 1 (BCLAF1), which is known to be toxic when over-expressed, was identified as a proteolytic target of caspase-10. The authors found that BCLAF1, which binds BCL-2, accumulates following caspase-10 inhibition, leading to autophagy induction due to the displacement of the autophagy-inducing protein beclin-1 from BCL-2.

This study shows that caspase-10 is required to maintain a basal level of autophagy essential for myeloma survival, whereas inhibition of caspase-10 induces autophagic cell death, which could be exploited therapeutically. MT

Large non-coding RNA in pluripotency

Transcription factors and microRNAs (miRNAs) act in concert to modulate the pluripotency state of embryonic stem cells (ESCs). Among the miRNAs that are expressed in the pluripotent state, several have been shown to target core pluripotency factors; for example, miR-145 targets Sox2, Oct4 and Nanog. These miRNAs were suggested to participate in the downregulation of the pluripotency state when ESCs undergo differentiation, but it has been unclear how their effects are limited in the pluripotent state. Liu and colleagues (*Dev. Cell* http://doi.org/k7b; 2013) have found that a large intergenic non-coding RNA, linc-RoR, is expressed in the pluripotent state and acts as an endogenous competitor by sharing target sites for miRNAs with pluripotency factors, thus sequestering miRNAs away from their targets. The authors found that ectopic expression of linc-RoR increases the expression of the pluripotency factors, whereas knockdown has the reverse effect and decreases pluripotency. They showed that linc-RoR acts at the post-transcriptional level and, using cells defective for miRNA processing, they demonstrate that the effects of linc-RoR are dependent on miRNA production. They observed that miR-145 inhibition rescues the expression of the core transcription factors when linc-RoR is silenced, and that mutating the miR-145 binding site within linc-RoR prevents it from maintaining pluripotency factor expression. It will be interesting to investigate if linc-RoR can be used to modulate the outcome of directed differentiation and reprogramming experiments. NLB

FANCJ overcomes fork barriers

Mutations in FANCJ cause Fanconi anaemia, a cancer predisposition syndrome. Absence of FANCJ helicase activity causes sensitivity to replication inhibitors, but the molecular basis for this is unclear. Niedzwiedz and colleagues now demonstrate that FANCJ counteracts fork stalling in the presence of replication barriers and prevents chromatin compaction associated with perturbed replication (*J. Cell Biol.* **201,** 33–48; 2013).

The authors find that FANCJ helicase activity is needed to facilitate replication in the presence of replication stress. Cells lacking FANCJ do not show altered stability of replication forks (unlike other Fanconi anaemia protein mutations), and the authors suggest that that the enzyme facilitates fork passage through sites that are hard to replicate. Supporting this idea, stabilization of G4 motifs, rare replication-resistant DNA structures, causes replication stalling in FANCJ-deficient cells. The absence of FANCJ causes the formation of single-strand DNA gaps, indicating that stalled replication forks skip over fork barriers on the lagging strand. Replication fork progression is coupled to chromatin maturation, and FANCJ-deficient cells are also found to contain more compact chromatin.

Replication stalling is known to stabilize the interaction of the histone chaperone Asf1 with the Mcm2-7 complex, and to locally increase the amount of newly synthesized histone H3. These features are enhanced in FANCJ-deficient cells, and the authors detect increased accumulation of H3 molecules with methylated lysines associated with heterochromatin at stalled forks, which could explain the effect on chromatin state. CKR

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