2-OGDDs, KDM6A showed low oxygen affinity in vitro, suggesting that it may act as a hypoxia sensor. Accordingly, removal of KDM6A reproduced the inhibitory effects of hypoxia on myoblast differentiation, whereas expression of a KDM6A variant with enhanced oxygen affinity (which is thereby less sensitive to hypoxia) rescued myoblast differentiation under hypoxia. Thus, KDM6A is directly inhibited in low oxygen conditions, which drives hypoxia-associated H3K27 hypermethylation.

Batie et al. observed that H3K4me3 — a modification that typically activates gene expression — was increased at genomic loci of hypoxia-responsive genes and this substantially preceded active transcription. Thus, hypoxia-induced changes in histone methylation predispose the chromatin for a robust hypoxic response.

Mechanistically, KDM5A depletion in HeLa cells — by increasing H3K4me3 levels and inducing hypoxia-responsive genes — mimicked the effect of hypoxia. Proteomic analysis revealed that KDM5A is one of the most highly expressed KDM5 family members in HeLa cells. Furthermore, Chakraborty et al. found that, similarly to KDM6A, KDM5A has low oxygen affinity. These data collectively indicate that KDM6A and KDM5A — and perhaps also other KDMs — are direct sensors of hypoxia and that their inhibition in low oxygen conditions modulates gene expression in hypoxia.

In the future, it will be interesting to investigate the role of this direct modulation of chromatin by hypoxia in vivo, where oxygen levels can largely vary. In particular, KDM-mediated gene regulation could be important in cellular environments known to experience hypoxia, including developing embryos, stem cell niches and the inner mass of tumours.

Paulina Strzyz

ORIGINAL ARTICLES Batie, M. et al. Hypoxia induces rapid changes to histone methylation and reprograms chromatin. *Science* **363**, 1222–1226 (2019) | Chakraborty, A. A. et al. Histone demethylase KDM6A directly senses oxygen to control chromatin and cell fate. *Science* **363**, 1217–1222 (2019)

expression, activated in response to proteasome inhibition. Thus, sequence editing of SKN-1A by removal of N-glycans from asparagine is required for the regulation of proteasome-encoding genes. The authors speculate that aspartates might be required for the binding of specific cofactors necessary for the transcriptional activation of proteasome-encoding genes; however, how protein editing alters SKN-1A transcriptional activity remains to be determined.

This study uncovers an unusual mechanism by which SKN-1A is activated to increase proteasome subunit synthesis. In normal conditions, SKN-1A is anchored to the ER through its N-terminal domain, where it is glycosylated and then released from the ER for proteasomal degradation, which keeps SKN-1A levels low. When proteasome function is impaired, SKN-1A is cleaved and deglycosylated, which confers specificity towards proteasome-encoding genes. The authors show that SKN-1C, which is not localized to the ER and does not undergo such editing, regulates a distinct transcriptional programme (a response to oxidative stress).

Compromised proteasome activity reduces cell viability and is detrimental to the organism. Here, the authors show that markedly increasing the expression of proteasome subunits by overexpressing active aspartate-containing truncated SKN-1A partially protected worms from adult-onset paralysis induced by the accumulation of amyloid aggregates. These findings support the hypothesis that increasing proteasome subunit expression can boost proteostasis.

Kim Baumann

ORIGINAL ARTICLE Lehrbach, N. J. et al. Protein sequence editing of SKN-1A/Nrf1 by peptide: N-glycanase controls proteasome gene expression. *Cell* **177**, 737–750 (2019)
FURTHER READING Rousseau, A. & Bertolotti, A. Regulation of proteasome assembly and activity in health and disease. *Nat. Rev. Mol. Cell Biol.* **19**, 697–712 (2018)

Journal Club

THE PRINCIPLES OF SPINDLE BIPOLARITY

I was a PhD student when I first read the Heald et al. article on the assembly of bipolar spindles around artificial chromosomes. Although it was known that mitosis in plants and meiosis in most animal species occurred in the absence of centrosomes, Heald et al. demonstrated that DNA-coated beads were sufficient to induce the formation of microtubule arrays that self-organized into bipolar spindles. Going back to this article, I was reminded of the power of simplified systems to address complex biological questions.

The cues that drive spindle bipolarity in somatic cells were thought to originate from the centrosomes and from centromeric DNA sequences that direct the assembly of kinetochores. To test the importance of centromeric DNA in this process, Heald et al. developed a simplified in vitro system in which magnetic beads were coated with plasmid DNA that did not contain centromeric DNA and therefore could not assemble kinetochores. When incubated with interphase *Xenopus* egg extracts, these beads assembled into chromatin that was able to replicate and promote the assembly of a functional nuclear envelope. In the presence of mitotic extracts and fluorescently labelled tubulin, spindle-like structures assembled from chromatin beads, demonstrating that neither centrosomes nor kinetochores are essential bipolarity cues.

Temporal analyses of this process uncovered three distinct phases: a first phase of nucleation, in which microtubule arrays extend radially; a second phase of coalescence, during which microtubules form compact bundles around chromatin; and a third phase of bipolarity establishment, characterized by the appearance of two focused poles that require the minus-end microtubule motor dynein. Fluorescently labelled microtubule seeds revealed that during nucleation microtubules display random polarity. By contrast, when spindles became bipolar, microtubule polarity was uniform with their minus ends leading towards the poles. The authors proposed that bipolarity arises from cytoplasmic asymmetry introduced by chromatin that favours microtubule nucleation, the intrinsic polarity of microtubules and the activity of motors leading to microtubule sorting into bipolar arrays of uniform polarity.

Heald et al. suggested that chromatin is not a conventional microtubule nucleation site but instead locally changes the cytoplasm in favour of microtubule nucleation. Interestingly, it turns out that this could be a more general characteristic of microtubule organizing centres (MTOCs) than anticipated. Indeed, as recently shown by Woodruff et al., centrosomes can locally increase tubulin concentration, thereby promoting microtubule nucleation. A closer look at how different MTOCs regulate local properties that regulate microtubule nucleation is likely to shed light on this fascinating mechanism.

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ORIGINAL ARTICLES Heald, R. et al. Self-organization of microtubules into bipolar spindles around artificial chromosomes in *Xenopus* egg extracts. *Nature* **382**, 420–425 (1996) | Woodruff, J. B. et al. The centrosome is a selective condensate that nucleates microtubules by concentrating tubulin. *Cell* **169**, 1066–1077 (2017)