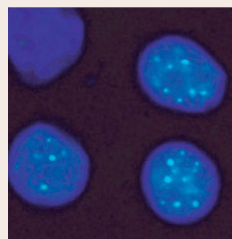


### Histone phosphorylation dawns at methylated DNA

Post-translational histone modifications – histone codes – specify local chromatin environments that control chromosome function during the

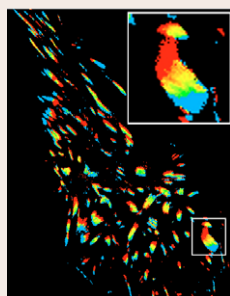
cell cycle. Widespread phosphorylation of histone H3 during mitosis by the kinase Aurora B, for example, helps ensure accurate chromosome segregation. However, in G2 phase, H3 phosphorylation occurs only at pericentromeres (heterochromatin domains near the centromeres) because Aurora B is restricted to this region. Karine Monier and co-authors now report that DNA methylation promotes this pattern (see p. 101). The authors show that histone H3 phosphorylation at pericentromeres starts in late S phase, persists into G2 phase and requires Aurora B activity. Using immunofluorescence in situ hybridization, they show that Aurora B and phosphorylated histone H3 are more abundant at large pericentromeres (where there is a high density of methyl cytosine) than at small ones. Finally, they report that disruption of DNA methylation prevents the localization of Aurora B to pericentromeres. Thus, the authors conclude, DNA methylation targets Aurora B to pericentromeres during interphase. Because tumour cells are often hypomethylated, they propose that mislocalization of Aurora B could contribute to chromosomal instability in cancer.



### Speckles mark the spot for DNA repair

Metabolites and environmental agents continuously damage DNA; so, to avoid genomic instability,

cells have DNA repair pathways that deal with different types of DNA lesion. Base excision repair (BER), for example, removes 8-oxoguanine and other modified bases produced by oxidative stress. Pablo Radicella and colleagues now reveal that UVA irradiation induces the relocalization of the first two enzymes in this pathway – the DNA glycosylase hOGG1, which recognizes 8-oxoguanine, and the abasic endonuclease APE1 – to nuclear speckles, organelles involved in transcription and mRNA splicing (see p. 23). The authors show that the UVA-induced relocalization of hOGG1, which is homogeneously distributed in the nucleoplasm of untreated cells, does not depend on its recognition of 8-oxoguanine. Instead, they report, reactive oxygen species (ROS) induced by UVA irradiation provide the signal. Given that nuclear speckles are associated with the opening up of chromatin, the authors propose that these organelles might play a direct role in BER by helping components of the pathway to access damaged DNA.



### Paxillin makes the switch

Three types of integrin-based adhesion connect cells to the extracellular matrix: focal complexes (FXs) drive cell spreading and migration; focal adhesions (FAs)

mediate robust adhesion to the matrix; and fibrillar adhesions (FBs) mediate matrix remodelling. But what regulates the distribution and dynamics of these interconvertible adhesions? On p. 137 Ronen Zaidel-Bar and co-authors report that tyrosine phosphorylation of the FA-associated adaptor protein paxillin acts as a major switch in their regulation. The authors use live-cell imaging to show that tyrosine-phosphorylated paxillin is associated with FXs and FAs but absent from FBs and that mechanical force negatively regulates the proportion of paxillin that is phosphorylated. Overexpression of a non-phosphorylatable mutant of paxillin enhances FB formation, they report, whereas overexpression of a phosphomimetic mutant induces FX and FA formation. The phosphomimetic mutant also enhances adhesion turnover, probably by recruiting focal adhesion kinase (FAK). The authors use these data to construct a model in which paxillin phosphorylation, FAK and mechanical forces concertedly regulate the assembly and turnover of integrin-based adhesions.

### NOne-stop respiration

The signalling molecule nitric oxide (NO) helps to regulate blood flow, nerve transmission and cellular defence. It might also regulate cellular respiration by inhibiting cytochrome c oxidase (CcO) – a component of the mitochondrial electron transport chain. On p. 160, Salvador Moncada and co-authors report that CcO can maintain mitochondrial respiration even when partly inhibited by NO by increasing its electron turnover. The authors use a visible-light spectroscopy system to measure O<sub>2</sub> and NO concentrations, mitochondrial respiration, and

cytochrome redox states in cells genetically modified to produce NO when treated with arginine. Their results show that although endogenously generated NO affects the redox state of cytochromes – it increases their reduction by inhibiting CcO – respiration is not inhibited until this reaches a critical point. Respiration continues unabated until then, they report, because of an increased flux of electrons through uninhibited NO-free CcO. This physiological mechanism, the authors suggest, enables cells to maintain their respiration without compromising their bioenergetic state when the cellular O<sub>2</sub>:NO ratio changes in response to different types of stress – for example, hypoxia.



### Telling tails on chromatin and lamins

Nuclear lamins form a web-like lamina beneath the nuclear envelope. They are closely associated with chromosomes, so could regulate chromatin organization and consequently gene expression. Yosef Gruenbaum and colleagues have characterized conserved sequences in *Drosophila* and *C. elegans* lamins that might mediate this association (see p. 77). A region in the tail domain of the *Drosophila* B-type lamin Dm0 binds to chromatin in vitro by interacting with histone H2A. The authors now report that a nuclear localization

sequence (NLS) and a TRAT motif in this region are both required for lamin Dm0 to bind to chromosomes. This binding requires both threonine residues in the TRAT motif, which indicates that it might be regulated by phosphorylation. The authors also show that the NLS in lamin Dm0 and nematode lamin is required for binding to histone H2A in vitro and that lamin Dm0 only binds to histone H2A that contains its N- and C-tail domains. These new details about chromatin-lamin interactions provide new insights into human laminopathies, since these diseases are characterized by changes in both nuclear architecture and gene regulation.

### Development in press

#### Foxo3a: support signal for ovaries

During mammalian oestrous cycles, ovarian follicles support the development and release of oocytes. But this is not just one-way support, as oocytes also contribute to follicle development. In a paper published in *Development*, Liu and colleagues report that oocyte-specific expression of the transcription factor Foxo3a negatively regulates oocyte growth and follicular development. The researchers' previous work had suggested that the suppression of Foxo3a in oocytes – through activation of the PI 3-kinase pathway – might be needed for follicular development and oocyte growth. To test this idea, they generated transgenic mice that express constitutively active Foxo3a in their oocytes. The female transgenic mice, they report, are infertile because of retarded oocyte growth and follicular development, and anovulation. They also show that constitutively active Foxo3a causes reduced oocyte-specific expression of proteins that are required for follicle development. Overall, the researchers conclude that Foxo3a is an important intra-oocyte signalling molecule and suggest that their results might provide clues to the causes of premature ovarian failure in humans.

Liu, L., Rajareddy, S., Reddy, P., Du, C., Jagarlamudi, K., Shen, Y., Gunnarsson, D., Selstam, G., Boman, K. and Liu, K. (2007). Infertility caused by retardation of follicular development in mice with oocyte-specific expression of Foxo3a. *Development* 134, 199-209.