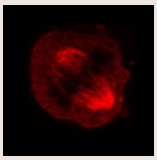
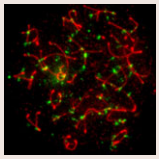
In this issue

By Jane Bradbury



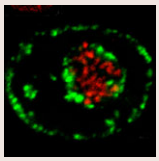
Breasting Aurora A's malignancy

Aurora A (serine/threonine kinase 6) is overexpressed in many pre-invasive and invasive breast carcinomas. High expression of Aurora A is strongly associated with decreased survival in patients with breast cancer, but the molecular mechanisms that underlie Aurora-A-associated malignancy are poorly understood. Here, Kavita Shah and co-workers (p. 2711) use a new chemical genetic approach to identify the pleckstrin-homology-like domain protein PHLDA1 as a putative Aurora A target. The authors confirm previous reports that PHLDA1 is frequently downregulated in primary breast cancers and, in addition, show that PHLDA1 downregulation is associated with oestrogen receptor expression in breast carcinoma. Aurora A directly phosphorylates PHLDA1, which leads to its degradation, but PHLDA1 also negatively regulates Aurora A, thereby setting up a feedback loop. Finally, they show that PHLDA1 upregulation and Aurora A inhibition act synergistically to promote cell death, and that PHLDA1 strongly inhibits the motility, proliferation and transformation of breast cancer cells. Thus, the authors suggest, PHLDA1 phosphorylation is one of the key ways in which Aurora A promotes breast malignancy. PHLDA1 overexpression could, therefore, provide a new way to modulate Aurora A deregulation in breast cancer.



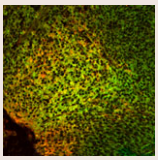
RAD18 mixes with meiosis

In mammalian somatic cells, the E3 ubiquitin ligase RAD18 is essential for cell survival after the induction of various types of DNA damage. This protein is best known for its role in mitotic cells in replication damage bypass, which allows the progression of DNA replication in the presence of DNA damage, and in double-strand break (DSB) repair. However, in spermatocytes, the expression level of RAD18 is highest in meiotic prophase, which suggests that it is also involved in meiosis. On page 2837, Willy Baarends and co-workers use *Rad18*-knockdown mice to determine the function of RAD18 in mammalian meiosis. They show that RAD18 is recruited to a specific subfraction of persistent meiotic DSBs in wild-type spermatocytes and to the chromatin of the XY chromosome pair, which forms the transcriptionally silent XY body. At the XY body, RAD18 mediates the chromatin association of its interaction partners, the ubiquitin-conjugating enzymes HR6A and HR6B. Moreover, RAD18 maintains meiotic sex chromosome inactivation by regulating histone H3 dimethylation. Finally, the authors show that RAD18 and HR6B are involved in the repair of a subset of meiotic DSBs. Together, these results indicate that RAD18 has a subtle role in DSB repair during meiosis.



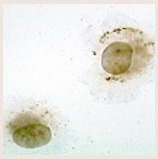
Ins and outs of rDNA replication

Nucleoli are specialized nuclear compartments in which several steps of ribosome biogenesis occur. Expressed rRNA genes – 20–50% of all rRNA genes in most human cells – coalesce in the nucleoli and are thought to replicate in early S phase; silent rRNA genes replicate in late S phase. Paradoxically, attempts to detect replicating rDNA inside nucleoli before mid S phase have failed. Here, Daniela Dimitrova (p. 2743) uses immunofluorescence microscopy to reveal the spatial and temporal dynamics of rDNA replication in HeLa cells. Early-replicating rDNA, she reports, is detectable at the nucleolar periphery and occasionally outside nucleoli, and then relocates to the nucleolar interior where it reassociates with the transcription factor UBF, which suggests that early-replicated rDNA mainly represents expressed rDNA. Intriguingly, contrary to the established model for active gene loci, replication initiates randomly throughout early-replicating rDNA. By contrast, mostly silent rDNA copies replicate inside the nucleoli during mid and late S phase from replication origins located in circumscribed regions of the non-transcribed intergenic spacers. The complex spatial dynamics of active and repressed rRNA genes during S phase, suggests Dimitrova, ensures efficient rDNA replication and maintenance of rDNA integrity.



MET signals for a thoughtful brain

GABAergic interneurons in the cerebral cortex have important roles in information processing by regulating the function and output of excitatory neurons. Several cognitive disorders (for example, epilepsy) have been linked to defects in these interneurons. Because some of these cognitive disorders have a developmental component, it is important to understand the signals that control GABAergic interneuron development. Here, Carlos Inbáñez and colleagues (p. 2797) provide new insights into the control of the differentiation and migration of GABAergic neuronal precursors in the mouse medial ganglionic eminence (MGE). GDNF (glial-cell-line-derived neurotrophic factor) and its GPI-anchored receptor GFRα1 are known to promote the differentiation and migration of immature interneurons. The authors now report that soluble GFRα1 also promotes these processes in MGE GABAergic neurons and that MET, a tyrosine kinase receptor previously implicated in GABAergic interneuron development, and its ligand hepatocyte growth factor (HGF) negatively regulate GDNF responses in the MGE. Together, these results suggest that there is an unknown transmembrane signalling partner for the GDNF–GFRα1 complex on GABAergic interneurons and uncover an unexpected interplay between GDNF–GFRα1 and HGF–MET signalling in the development of these cells.



miR-199a-3p, caveolin and cancer

MicroRNAs (miRNAs) are small non-coding endogenous RNA molecules that regulate proliferation, apoptosis and other cellular processes by modulating the expression of various target genes. Recently, some studies have suggested that miRNAs are involved in cancer pathogenesis. miR-199a-3p, for example, is highly expressed in some tumour cells (including breast cancer cells) but underexpressed in others. On page 2826, Burton Yang and colleagues begin to unravel the role that miR-199a-3p has in cancer cells. The authors show that miR-199a-3p expression promotes the proliferation and survival of rat endothelial cells and of two human breast cancer cell lines. Using bioinformatics, they identify caveolin-2 as a potential target of miR-199a-3p; caveolins are structural proteins that, by organizing caveolae, help to regulate endocytosis and cell signalling. miR-199a-3p expression, the authors report, inhibits the expression of endogenous caveolin-2 and of a reporter construct containing the 3′UTR of caveolin-2. Importantly, overexpression of caveolin-2 counteracts miR-199a-3p-mediated effects on cell proliferation and increases breast cancer cell survival after treatment with the anticancer drug docetaxol. The authors suggest, therefore, that miR-199a-3p is involved in breast cancer progression and represents a potential target for anticancer therapies.

Development in press

Feel the force: embryonic bone shaping

The vertebrate skeleton contains more than 200 bones, each with its own unique shape, size and function. Postnatally, bones remodel in response to the muscle forces they encounter. So bed rest, for example, can result in bone thinning. Now, Amnon Sharir, Elazar Zelzer and colleagues report in *Development* that in mice muscle force also regulates bone shaping during embryogenesis. Using micro-computed tomography scans of embryonic long bones, the researchers identify a new developmental programme that, through asymmetric mineral deposition and transient cortical thickening, regulates the specific circumferential shape of each bone. This programme of preferential bone growth, they report, ensures that each bone acquires an optimal load-bearing capacity. Moreover, the programme is regulated by intrauterine muscle contractions; in a mouse strain that lacks such contractions, the bones lose their stereotypical circumferential outline and are mechanically inferior. Thus, the researchers suggest, a reciprocal relationship between structure and mechanical load in utero determines the 3D morphology of developing bones.

Sharir, A., Stern, T., Rot, C., Shahar, R. and Zelzer, E. (2011). Muscle force regulates bone shaping for optimal load-bearing capacity during embryogenesis. *Development* **138**, 3247-3259.