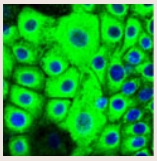
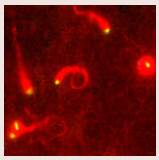
In this issue



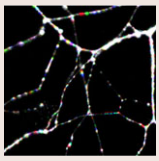
Let there be liver

Specifically directing stem cell differentiation to create different cell types is useful for the development of therapeutic approaches and pharmaceutical screens. By using chemical compounds, this has been done by Melanie Welham and colleagues (p. 1992), who describe a small-molecule inhibitor of glycogen synthase kinase 3 (GSK3) that can drive differentiation of human embryonic stem cells (hESCs) into definitive endoderm with hepatic potential. In mouse ESCs, inhibition of GSK3 leads to enhanced self-renewal. By contrast, treatment of hESCs with the GSK3 inhibitor 1m results in the opposite effect: 1m-treated hESCs induce a differentiation program. These cells initially form a state that resembles the primitive streak and then differentiate into mesoderm and endoderm, the authors observe. This loss of pluripotency is mediated by the activation of the Wnt–β-catenin pathway, and a rapid and transient upregulation of *NODAL* gene expression. In a further set of experiments, the authors show that prolonged GSK3 inhibition results in cells with hepatoblast characteristics and the 1m-induced definitive endoderm matures into hepatocyte-like cells. The authors hope that these results form the basis for the development of a useful therapy for liver failure, and provide a model system in which to study liver function and disease.



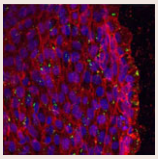
Actin bulks up

Regulation of actin and myosin II during the cell cycle controls the mechanical properties of cells and triggers changes in cell shape. Current models for cell mechanics focus primarily on actomyosin in the cell cortex where F-actin and myosin II interact, and ignore possible contributions from the bulk cytoplasm in cell-cycle-regulated shape change. Therefore, Christine Field, Timothy Mitchison and co-workers (p. 2096) explore how bulk cytoplasmic actomyosin in *Xenopus laevis* egg extracts is regulated during the cell cycle. The authors report that gelation-contraction – a process in which bulk actin polymerises, gels into a filament network and contracts under the influence of myosin II – occurs extensively in periodic waves during the mitotic phase, but not during interphase, in a Cdk1-dependent manner. Furthermore, the authors report that actin nucleation, rather than actin disassembly and myosin II activity, is likely to be the most crucial factor for cell cycle regulation. The authors additionally demonstrate, by using live zebrafish embryos, that in vivo actin polymerisation around vesicles in the bulk cytoplasm is greatly enhanced during mitosis, which is consistent with enhanced nucleation. F-actin polymerisation in bulk cytoplasm appears, therefore, to be cell cycle regulated in early vertebrate embryos. Further studies should, the authors propose, elucidate additional details on the biophysics and regulation of actomyosin in the bulk cytoplasm.



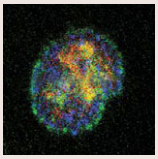
(Star)gazin' into the neurite

Stargazin-like γ-subunit proteins are surrounded by controversy: whereas they were previously thought to be subunits of Ca^{2+} channels, they are now widely accepted to belong to a group of transmembrane AMPA receptor regulatory proteins (TARPs). In addition, their cellular roles are still largely unclear. In their study on p. 2049, Annette Dolphin and colleagues now provide evidence that stargazin-like γ-subunit proteins have a role in endosomal trafficking and neurite outgrowth in neuronal cells. The authors show that, in sympathetic cervical ganglion neurons, the stargazin-like γ_7 subunit (γ_7) localises to small vesicular organelles. These vesicles primarily move in a retrograde direction and do not contain markers for the ER, Golgi, mitochondria, lysosomes or late endosomes. Instead, vesicular γ_7 colocalises with the early-endosome marker EEA1 and the nerve growth factor receptor TrkA, suggesting it is a component of signalling endosomes. Furthermore, in cultured neuronal cells, knockdown of endogenous γ_7 with small hairpin RNA decreases neurite length. In combination with the previous observation that transport of activated growth factor receptors to the neuronal cell body is essential for neurite outgrowth, these results suggest that the presence of γ_7 in signalling endosomes is important in the regulation of this process.



Cadherins close the gap

N-cadherin and E-cadherin are members of the cadherin family of homophilic cell–cell adhesion molecules that mediates actin-dependent contact between adjacent cells. N-cadherin and E-cadherin localise to membrane ruffles, such as lamellipodia, and are internalised within macropinosomes (large endocytic vesicles that form in membrane ruffles), suggesting that they are involved in macropinosome formation. However, until now, this potential role for cadherins in macropinocytosis remained undetermined. Here, Michelle Bendeck and colleagues (p. 2013) describe a new mechanism whereby E-cadherin or N-cadherin coordinates the recruitment of cadherin molecules to membrane ruffles and promotes closure of the vesicle membrane to form the macropinosome. The authors show that N-cadherin localises to sites of cell-autonomous membrane overlap in areas of membrane ruffling. In addition, both N-cadherin and E-cadherin promote macropinocytosis in cells stimulated with growth factor. The authors also suggest that these proteins facilitate closure of vesicles to form macropinosomes through cadherin homophilic interactions at membrane adhesions. Therefore, their findings indicate that cadherins – rather than solely acting as adhesion molecules – have a crucial role in the regulation of cell migration during wound healing, the innate immune response and gastrulation.



Y RNAs give license to copy

DNA replication is a complex process that involves numerous proteins. In addition, a group of 69- to 112-nucleotide-long, stem-loop, non-coding RNAs (known as Y RNAs) have an important role in this process: in mammals, they are essential for replication initiation in nuclei. But how does Y RNA result in the initiation of replication? On p. 2058, Torsten Krude and colleagues now shed light on the molecular mechanisms behind these events. During late G1 phase, Y RNAs specifically associate with unreplicated euchromatin, and the authors find that this selective binding is driven by the lower stem and loop domains of the Y RNA molecules. By contrast, in nuclei that have entered G2 phase, most Y RNAs are displaced from chromatin. Using pull-down and colocalisation assays, the authors go on to show that, at initiation sites, Y RNAs interact with proteins involved in initiating DNA replication – such as the subunits of the origin recognition complex (ORC), the chromatin licensing and DNA replication factors Cdt1 and Cdt6, and the DNA unwinding element binding protein (DUE-B). Proteins that belong to the DNA replication elongation machinery and to sites of replicated DNA, however, do not associate or colocalise with Y RNAs. Therefore, the authors conclude that, by binding to unreplicated chromatin, Y RNAs act as licensing factors that are required for replication initiation but do not have a role in chain elongation.

Development in press

Stem cell development goes live

Stem cells are maintained by signals from their local microenvironment but it has been hard to study exactly how stem cell behaviour is controlled. In *Development*, Lucy Morris and Allan Spradling now describe a culture method for live imaging *Drosophila* ovarian development within the germarium and use it to test some long-held beliefs about ovarian follicle development. The germarium is a structure at the anterior tip of ovarioles that produces new ovarian follicles by controlling follicle and germline stem cell (GSC) division and nurturing their developing daughters. The researchers confirm, for example, that GSC divisions are oriented with respect to the anteroposterior axis of the germarium. They also show that somatic escort cells (the glial-like partners of early germ cells) do not adhere to and migrate with GSC daughters as previously proposed, but pass the GSC daughters from one escort cell to the next using dynamic membrane activity. These and other results establish the live imaging system as a valuable tool for the study of stem cell biology.

Morris, L. X. and Spradling, A. C. (2011). Long-term live imaging provides new insight into stem cell regulation and germline-soma coordination in the *Drosophila* ovary. *Development* **138**, 2207-2215.