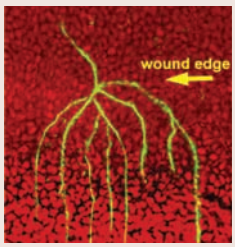
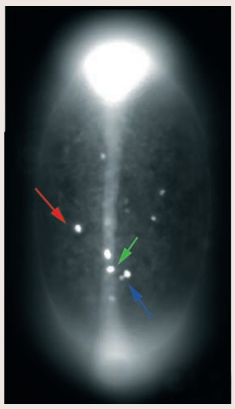
# In this issue

by Jane Bradbury



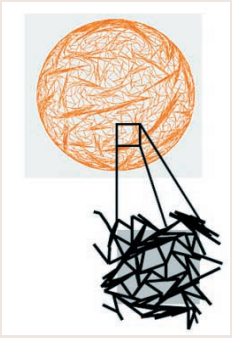

## Electric aid to wound healing

Small electric fields (EFs) can direct cell growth and migration in vitro. But, although similar EFs occur in developing embryos and near to healing wounds, no-one has shown that they have a physiological effect at the single-cell level in vivo. On p. 4681, Song et al. remedy this situation by showing that nerve regeneration and wound healing are stimulated and directed by an endogenously generated EF in wounded rat cornea. In the corneal epithelium, normal ion movements establish a transcorneal potential difference (TCPD) of about 40 mV. When wounded, the corneal epithelium instantaneously short-circuits and the TCPD drops to zero at the wound site, setting up a lateral endogenous EF in the epithelium. The authors show that drugs that increase the TCPD (and consequently the EF produced after corneal wounding) enhance the extent and direction of nerve sprouting and the rate of epithelial wound healing; drugs that reduce the TCPD have the opposite effect. These results have clinical implications for both wound healing and nerve regeneration.



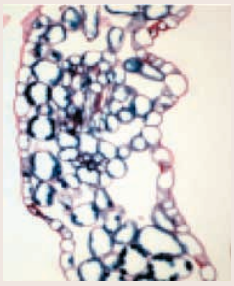
## Signal change in migration

In many organisms, primordial germ cells (PGCs) migrate to the gonad in response to directional cues from surrounding somatic tissues. In this example of directed cell migration, as in the others that occur during development, the migrating cell has to transduce extracellular cues intracellularly into directional migration. On p. 4787, Erez Raz and colleagues investigate the signalling pathways downstream of the cues provided by the ligand SDF-1a and its receptor CXCR4b during zebrafish PGC migration. By tracking GFP-tagged PGCs, the authors show that inhibition of G-protein-dependent signalling prevents PGCs reaching their normal target, which is what happens if CXCR4b is lost. Inhibition of phosphoinositide 3-kinase (PI3K) signalling, however, does not prevent PGCs reaching their target but slows down their migration and reduces the stability of filopodia. Furthermore, unlike in cell types in which PI3K activity controls directional cell migration (e.g. neutrophils), the PI3K products phosphatidylinositol (3,4,5)-trisphosphate and phosphatidylinositol (3,4)-bisphosphate are not polarized in zebrafish PGCs. Thus, although G-protein-dependent signalling is essential for directional migration of PGCs, PI3K signalling plays a permissive role, controlling overall motility rather than directing migration.



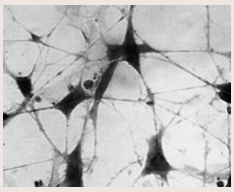
## A nuclear shock absorber

Cells respond to mechanical cues from their environment in part through changes in gene expression. But how is an external force transmitted to the genome? One possibility is that the stiffness of the nuclear envelope, which is physically connected to the chromatin through a network of lamin filaments, is involved in force transmission. By osmotically swelling *Xenopus* oocytes, Dennis Discher and colleagueshave devised an experimental system in which the mechanical properties of the intact nuclear envelope (membranes, pore complexes and the underlying lamin network) can be studied without interference from chromatin or nucleoplasm (see p. 4779). Their studies reveal that although the oocyte nuclear envelope is elastic – it can be expanded to twice its original area – it cannot be compressed below its normal size. The authors propose that the nuclear lamina in oocytes (and probably somatic cells) forms a network of interconnected rigid rods that acts as a molecular shock absorber. This model helps to explain the changes in nuclear mechanical properties seen in laminopathies.



## Lightening up leafy borders

Variegated plants, much prized by gardeners for their attractively patterned leaves, can arise through the formation of defective chloroplasts in some cells as a consequence of stable, loss-of-function mutations in nuclear genes. Sometimes, variegation is accompanied by perturbed leaf development. On p. 4807, John Mundy and co-workers investigate an *Arabidopsis* mutant of this type – the stable, recessive *variegated 3* (*var3*) mutant. They report that the yellow leaf areas of this mutant lack chloroplasts or contain developmentally retarded plastids and have reduced numbers of palisade cells, the elongated parenchymal cells found below the upper leaf surface. They have also isolated the *VAR3* gene, which encodes a novel zinc-finger protein, and show that VAR3 interacts with NCED4, a chloroplast-localized carotenoid dioxygenase. On the basis of these and other data, the authors propose that VAR3 is part of a protein complex that functions in a metabolic pathway required for chloroplast development and that the palisade cell defects in *var3* leaves are a secondary effect owing to incomplete chloroplast development.



## NO takes the Myc

Nitric oxide (NO) is a negative regulator of proliferation in many cell types, including neural cell precursors, in which it promotes neuronal differentiation. By contrast, the proto-oncoprotein N-Myc promotes proliferation of neuronal precursors and is downregulated in neuroblastoma cells induced to differentiate by retinoic acid. This prompted Elisabetta Ciani and colleagues to ask whether the antiproliferative action of NO in neuronal precursors is mediated by negative regulation of N-Myc expression(see p. 4727). They show that increasing NO levels in retinoic-acid-treated neuroblastoma cells, by overexpressing neuronal NO synthase (nNOS) or exposing the cells to an exogenous NO source, slows down their proliferation, accelerates their differentiation, and decreases N-Myc expression. Conversely, nNOS inhibition in cerebellar granule cell cultures increases both neuronal precursor proliferation and N-Myc expression. The authors conclude that NO regulates a switch in neuronal precursor programming, from proliferation to differentiation, through N-Myc and suggest that this new function for NO could provide a therapeutic target for the treatment of aggressive N-Myc-expressing neuroblastomas.

## *Development* in press

### Gasping for air

Early embryos get the oxygen they need for metabolism by diffusion. After gastrulation, however, efficient oxygen delivery requires a cardiovascular system. Reporting in *Development*, Ramírez-Bergeron and colleagues have used a mouse embryonic stem (ES) cell culture system to show that hypoxic responses are important for establishing the early mesoderm and its differentiation into haemangioblasts – bipotential precursors of endothelial and haematopoietic cells. They report that hypoxia accelerates the expression of Brachyury (a mesoderm-patterning factor), BMP4 (a mesoderm-promoting growth factor) and FLK1 (the receptor for vascular endothelial growth factor and a marker for haemangioblasts). This response depends on hypoxia-inducible factor (HIF), since ES cells lacking the HIF subunit aryl hydrocarbon receptor nuclear translocator (ARNT) produce fewer $FLK1^{+}$ cells in normoxic and hypoxic conditions. Ramírez-Bergeron and colleagues conclude that ineffective responses to hypoxia underlie the previously observed failure of $Arnt^{-/-}$ embryos to form a functional cardiovascular system.

**Ramírez-Bergeron, D. L., Runge, A., Cowden Dahl, K. D., Fehling, H. J., Keller, G. and Simon, M. C.** (2004). Hypoxia affects mesoderm and enhances hemangioblast specification during early development. *Development* **131**, 4623-4634.