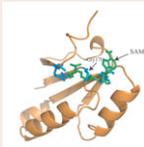
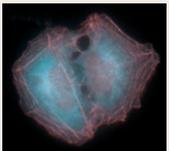


In this issue

**A new mitochondrial methyltransferase?**

Defects in the components or regulatory factors of mitochondrial complexes can cause diseases with wide-ranging phenotypes. Although mitochondrial diseases associated with complex I (CI) dysfunction are common, CI remains the least well-defined complex of the electron transport chain owing to its large size and complexity. Ricardo Escalante and colleagues recently identified the mitochondrial protein MidA, which is conserved between *Dictyostelium* and humans. On page 1674, they report additional findings suggesting that this protein regulates CI stability and/or function. *Dictyostelium midA* cells show a 50% decrease in CI activity, and knockdown of MidA expression in HEK293T cells decreases the amount of assembled CI. In addition, a yeast-two-hybrid assay shows that MidA interacts with the CI subunit NDUFS2. Bioinformatics approaches predict that MidA acts as a methyltransferase and identify the glycine residue(s) that are important for this activity. Furthermore, site-directed mutagenesis experiments confirm the importance of the putative methyltransferase domain for MidA function. Therefore, methylation of CI seems to be important for its function. In addition, the phenotype of *Dictyostelium midA* cells – which display characteristics including defects in development and phototaxis – emphasises the complex pathology underlying CI-related mitochondrial diseases.

**Quantifying mRNA in space and time**

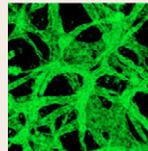
Regulation of eukaryotic gene expression occurs at multiple levels, and can vary depending on the gene. For example, the subcellular expression of β -actin is controlled by the localisation of its mRNA to actin-rich peripheral regions of migrating cells. On page 1761, Yaron Shav-Tal and colleagues report a novel system for spatio-temporal quantification of β -actin expression. They create a human cell line expressing a transcriptionally inducible form of the chicken β -actin gene (*ACTB*) that enables visualisation of the gene, the transcribed mRNA and the translated protein in individual cells. They first show that the rtTA transcription factor binds to the *ACTB* promoter only transiently, for an average of 40 seconds. Four-dimensional imaging shows that, in this inducible system, the rate of transcription gradually increases to a maximum after ~1 hour, then gradually decreases. In agreement with previous findings, the authors also report that β -actin mRNA is elongated at a speed of 3.3 kb/minute and, once exported from the nucleus, moves through the cytoplasm by diffusion. Notably, β -actin mRNA that is stimulated to localise to the cell periphery derives from a pre-existing mRNA pool, rather than from newly transcribed mRNA produced following induction. So, the initial localization of β -actin mRNA to the cell periphery is not coupled to the initiation of β -actin transcription in the nucleus. This is the first study to follow the complete cellular pathway of a protein-coding mammalian mRNA in live cells.

**Stress protection by DJ-1**

Mutations in DJ-1 (also known as PARK7) are associated with inherited Parkinson disease and neuronal death, although the underlying molecular mechanisms have been unclear. Given that DJ-1 is highly conserved, Simon Møller and colleagues investigated the cellular function of an *Arabidopsis thaliana* homologue of DJ-1, AtDJ-1a (p. 1644). They first show that AtDJ-1a expression increases in response to many types of stress, including excessive light exposure and oxidative stress. In addition, aging AtDJ-1a-null (but not young) plants suffer larger and more-frequent lesions than wild-type plants following stress exposure. Closer investigation reveals that these lesions occur owing to increased plant-cell death resembling cell death that occurs in human neurons expressing mutant DJ-1. At-DJ-1a is found to interact with and increase the activity of the copper-dependent enzymes CSD1 and AtGPX2, which decrease cellular levels of damaging reactive oxygen species (ROS). Furthermore, DJ-1 interacts with the human homologues of these enzymes (SOD1 and GPX2, respectively). The authors propose that DJ-1 mediates a protective effect in stressed cells through delivering copper to antioxidant enzymes, thereby promoting their activity and reducing cell death resulting from excessive ROS levels.

**ER export of GPI-anchored proteins**

Following their synthesis in the ER, many transmembrane proteins are selectively exported via interactions between their cytosolic domains and the Sec24 subunit of coat protein complex II (COPII) vesicles. By contrast, less is known about how GPI-anchored proteins (which lack a cytosolic domain) are exported from the ER in mammalian cells. Although the mechanisms of early secretory transport have been partially worked out in yeast, only recently is the picture becoming clearer for mammalian cells. On page 1705, Hans-Peter Hauri and colleagues add to this story through studying the transport of endogenous GPI-anchored proteins in HeLa cells. They first show that ER-to-Golgi transport of GPI-anchored proteins in human cells requires COPII and, more specifically, the Sec24 isoforms C and D. On the basis of studies in yeast, the authors test whether members of the p24 protein family (comprising p23, p24 and p25 in mammalian cells) are involved in this process: indeed, p23 and p24, but not p25, interact with and are required for the export of GPI-anchored proteins from the ER. By contrast, p24 proteins are not required for the transport of transferrin receptor, a type I transmembrane protein. Finally, the finding that p23 and p24 partially co-partition with GPI-anchored proteins in detergent-resistant membrane fractions suggests that lipid rafts are involved in the selective transport of GPI-anchored proteins from the ER.

**BMP-9 boosts endothelial cells**

Identifying the factors that regulate vasculogenesis and angiogenesis is of key therapeutic importance, as dysregulation of these processes can contribute to many types of human disease. Bone morphogenetic proteins (BMPs), which are members of the TGF β protein family, are known to be involved in the development and homeostasis of vascular systems. On page 1684, Tetsuro Watabe and colleagues (p. 1684) uncover a specific role for BMP-9 in promoting endothelial-cell proliferation. In contrast to previously published findings that suggest an inhibitory role for BMP-9, they show here using various approaches that this factor promotes vasculogenesis and angiogenesis *ex vivo* and *in vivo*. Furthermore, addition of exogenous BMP-9 increases the number of endothelial cells obtained when VEGFR2⁺ progenitor cells are differentiated *in vitro*. siRNA knockdown and overexpression studies show that this increase in endothelial-cell yield is mediated by BMP-9-mediated activation of activin-receptor-like kinase 1 (ALK-1), which is known to be preferentially expressed by endothelial cells. BMP-9-ALK-1 signalling activates downstream VEGF-VEGFR2 and Ang-1-Tie2 pathways, both of which are known to contribute to angiogenesis. These data increase our understanding of how BMPs influence vasculogenesis and angiogenesis, and suggest that BMP-9 is a therapeutic target for diseases in which these processes are dysregulated.

Development in press**Sunspot shines new light on Wnt signalling**

In many organisms, the Wingless (Wg)/Wnt signalling pathway regulates developmental processes through Armadillo (Arm)/ β -catenin, which activates target gene transcription through the TCF transcription factor family. In a study published in *Development*, Tetsu Akiyama and colleagues identify a new interaction partner for Arm in *Drosophila*, called Sunspot (Ssp), which acts independently of dTCF. Using mutant fly lines, the researchers report that Ssp is required for the proliferation of imaginal disc cells, salivary glands and the central nervous system in fly larvae. Ssp controls the transcription of genes involved in proliferation, they report, but, although this requires Arm, it is independent of dTCF. By using overexpression studies, the authors also show that Wg negatively regulates Ssp signalling by controlling its subcellular location: Wg expression directs Ssp to the nuclear envelope, away from its targets, in a process that also requires Arm. Given that Wnt signalling is highly conserved, the researchers suggest that Ssp regulation by Wg and Arm is a general signalling mechanism.

Taniue, K., Nishida, A., Hamada, F., Sugie, A., Oda, T., Ui-Tei, K., Tabata, T. and Akiyama, T. (2010). Sunspot, a link between Wingless signaling and endoreplication in *Drosophila*. *Development* 137, 1755-1764.