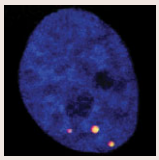
In this issue

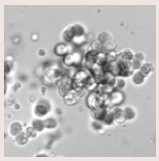
NEW ARTICLE SERIES: Stem Cells

In this issue, JCS is pleased to announce the launch of our new Article Series on Stem Cells. Stem cell research has emerged as one of the most exciting areas of cell biological and biomedical research in recent years. Numerous studies have greatly enhanced our understanding of the roles of stem cells in development, the factors that maintain pluripotency and drive tissue-specific differentiation, and the importance of the stem cell niche. However, progress has not only been made in understanding the fundamental mechanisms that underlie self-renewal and differentiation. As JCS Editor-in-Chief Fiona M. Watt highlights in her Editorial (p. 3527), the focus also lies on developing new stem-cell-based therapies to treat a variety of diseases. The series will be kicked off by two Cell Science at a Glance articles that aim to highlight some of the key developments in the stem cell field. In this issue, Cristina Lo Celso and David Scadden (p. 3529) provide an overview of the haematopoeitic stem cell niche. In the next issue, Siim Pauklin, Roger Pedersen and Ludovic Vallier discuss the origins of mouse pluripotent stem cells and their defining features. Future articles in the Series on Stem Cells will cover topics such as direct reprogramming, the role of fibronectin in stem cell differentiation, and the importance of nuclear structure in stem cell maintenance and regulation.



Long telomeres without telomerase

Many tumour cells avoid senescence by activating telomerase, which prevents telomere shortening and facilitates unlimited proliferation. However, 10–15% of cancer cells maintain telomere length differently: the alternative lengthening of telomeres (ALT) pathway involves both DNA repair and recombination. ALT-associated promyelocytic leukaemia (PML) nuclear bodies (APBs) – unique nuclear structures that contain telomeres and proteins associated with them – are specifically found in cells that undergo ALT and colocalise with proteins involved in DNA repair and recombination. However, a direct link between APBs and telomere lengthening has not yet been shown. On page 3603, Karsten Rippe and colleagues now elucidate the steps involved in APB biogenesis and the induction of ALT. They show that enrichment at telomeres of the nuclear body components PML and Sp100, the SUMO E3 ligase MMS21 as well as SUMO1 itself, the recombination factor NBS1 or the shelterin subunits TRF1 and TRF2 can nucleate APB formation. Other proteins, such as the recombination factors Rad9, Rad17 and Rad51 are, however, secondarily recruited to the APB. Furthermore, the de novo assembly of APBs induces double-strand break repair and leads to telomere repeat extension, which suggests that ALT is regulated by a multi-step process of initiation, complex assembly, DNA repair and, finally, telomere elongation.

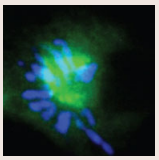


GCSF signalling: ROS joins in

Although large amounts of reactive oxygen species (ROS) can be detrimental to a cell, moderate levels are important for the regulation of various cellular processes. When produced in defined subcellular compartments, ROS act locally to specifically modulate signalling pathways and cellular responses, but the mechanisms that underlie such regulation have not yet been elucidated. On page 3695, Ivo Touw and colleagues now show that signalling from the granulocyte colony stimulating factor receptor (GCSFR) is affected by ROS, and that the ER-resident antioxidant peroxiredoxin 4 (PRDX4) and the protein tyrosine phosphatase 1b (PTP1B) are involved in this regulation. PRDX4 primarily resides in the ER and ER–Golgi intermediate compartments (ERGIC), and interacts with the cytoplasmic domain of activated GCSFRs on endosomes, thereby attenuating GCSF-induced STAT3 activation and proliferation in myeloid progenitors. The oxidation-sensitive phosphatase PTP1B also interacts with the GCSFR and inhibits GCSF-induced signalling from early endosomes by reducing the levels of receptor phosphorylation. PTP1B seems to be a downstream target of PRDX4, and the authors propose that, PRDX4 eliminates ROS, which – in turn – counteracts the inhibition of PTP1B by these molecules and, hence, leads to signal attenuation.

Phagocytosis: Rab35 makes the cup

Phagocytosis is a key process of the innate immune response. It involves highly orchestrated signalling events that drive remodelling of the actin cytoskeleton to form the phagocytic cup, and members of the Rho GTPase family are known to be important for this process. In addition, it has been shown that the small GTPase Rab35 is involved in endocytic processes and localises to phagosomal membranes. However, its precise role in phagocytosis remained unclear. On page 3557, Nobukazu Araki and co-workers now show that Rab35 is recruited to the phagocytic membrane following activation of the Fcγ receptor (FcγR) in macrophages and that it is required for FcγR-mediated phagocytosis. The expression of a dominant-negative Rab35, as well as its depletion by using shRNAs, inhibits FcγR-mediated phagocytosis. Furthermore, GTP-bound Rab35 associates with PtdIns(3,4,5)P_3-enriched membrane regions at the base of the phagocytic cup. There, the Ras-related protein is involved in actin disassembly and remodelling, processes that are required for the formation of a fully functional phagosome. In addition Rab35-GTP recruits ACAP2 – a GTPase-activating protein for the ADP-ribosylation factor ARF6 – to the phagocytic cup. Thus, the authors suggest that, following engagement of the FcγR, Rab35 regulates actin remodelling and membrane dynamics through modulating ARF6 activity.



FAT10 links inflammation and cancer

In the 19th century, Rudolph Virchow observed that tumours often arise at sites of chronic inflammation. By now it is well known that inflammation can indeed drive tumourigenesis. One of the molecules implicated in this process is the cytokine tumour necrosis factor-alpha (TNF-α), which is associated with the inflammatory immune response and exerts pro-tumourigenic signals through the activation of TNF receptor 1 (TNFR1). The nuclear factor kappa B (NF-κB) signalling pathway is activated by TNF-α and is a key mediator of the immune response. But is this pathway also involved in inflammation-induced tumourigenesis? Data presented on page 3665 by Caroline Lee and colleagues suggest that it is. TNF-α induces gene expression of FAT10 (officially known as *UBD*) through activation of the NF-κB pathway in two colorectal cell lines. FAT10 then leads to an abbreviated mitotic phase and inhibits the association of the spindle checkpoint protein Mad2 with the kinetochore. In addition, increased FAT10 gene expression results in genomic instability and an increase in the number of cells with abnormal chromosome numbers. Finally, the researchers report that FAT10 is involved in protecting cells against TNF-α-induced cell death. Taken together, these observations provide a mechanism for tumour formation following chronic inflammation and highlight a potential therapeutic target for the treatment of such cancers.

From *Development*

Endothelial cell movements during angiogenesis

During angiogenesis, new blood vessels sprout from an existing vascular network, elongate and bifurcate to form a new branching network. The individual and collective movements of vascular endothelial cells (ECs) during angiogenic morphogenesis are poorly understood but, in *Development*, Koichi Nishiyama and colleagues provide some new insights into these movements. Using time-lapse imaging and a computer-assisted analysis system to quantitatively characterise EC behaviours during sprouting angiogenesis, they show that ECs move backwards and forwards at different velocities and change their positions relative to each other, even at the tips of elongating branches in vitro. This 'cell mixing', which also occurs in vivo at the tips of developing mouse retinal vessels, is counter-regulated by EC–EC interplay through Dll4–Notch signalling and might be promoted through EC–mural cell interplay. Finally, the researchers show that the dynamic behaviour and migration of ECs contribute to effective branch elongation. Thus, cell behaviours during angiogenesis and other forms of branching morphogenesis might be more complex and variable than previously thought.

Arima, S., Nishiyama, K., Ko, T., Arima, Y., Hakozaki, Y., Sugihara, K., Koseki, H., Uchijima, Y., Kurihara, Y. and Kurihara, H. (2011). Angiogenic morphogenesis driven by dynamic and heterogeneous collective endothelial cell movement. *Development*, **138**, 4763-4776.