IN BRIEF

CANCER

Inactivating cholecystokinin-2 receptor inhibits progastrin-dependent colonic crypt fission, proliferation, and colorectal cancer in mice

Jin, G. *et al. J. Clin. Invest.* **119**, 2691–2701 (2009)

Overexpression of progastrin induces colonic hyperproliferation and promotes colorectal cancer in mice. This paper showed that the cholecystokinin 2 receptor (CCK2R; also known as CCKBR), which is the primary receptor for CCK and amidated gastrin, was upregulated in mice overexpressing human progastrin in a model of colorectal carcinogenesis. *Cck2r* deletion in these mice decreased aberrant crypt foci formation and reduced tumour size, highlighting the important role of CCK2R in mediating the effects of progastrin and the potential of this receptor as a therapeutic target for colorectal cancer.

VIRAL INFECTION

Essential role of platelet activating factor receptor in the pathogenesis of Dengue virus infection

Souza, D. G. *et al. Proc. Natl Acad. Sci. USA* **106**, 14138–14143 (2009)

The lack of specific treatments for severe dengue virus infection is a major burden on the health-care systems in the developing world. In this study, inoculation of adult mice with an adapted strain of Dengue virus caused a systemic disease, which was absent in mice lacking the platelet-activating factor receptor (PAFR). Treatment of wild-type mice with an orally active PAFR antagonist prevented thrombocytopoenia, haemoconcentration and hypotension, and decreased lethality, even when started 5 days after virus inoculation. So, PAFR antagonists could be disease-modifying agents in Dengue infection.

G PROTEIN-COUPLED RECEPTORS

Persistent cAMP-signals triggered by internalized G-protein-coupled receptors

Calebiro, D. *et al. PLoS Biol.* **7**, e1000172 (2009)

Sustained cyclic AMP production by parathyroid hormone receptor endocytosis

Ferrandon, S. *et al. Nature Chem. Biol.* 23 August 2009 (doi:10.1038/nchembio.206)

In the established view of G protein-coupled receptor (GPCR)-mediated signalling, removal of the receptor from the cell surface by endocytosis terminates the production of second messengers. Two recent papers question this paradigm by showing that GPCR-mediated cyclic AMP signalling can occur from intracellular sites. Calebiro and colleagues studied cAMP responses to thyroid-stimulating hormone (TSH) in thyroid follicles. TSH stimulation caused internalization of TSH receptors in close association with $G_{\alpha s}$ subunits and adenylyl cyclase 3. Receptors were internalized together with TSH and produced downstream cellular responses that were distinct from those triggered by cell surface receptors. Ferrandon and colleagues examined the effects of two parathyroid hormone (PTH) receptor ligands, $PTH_{1–34}$ and PTH-related peptide $(PTHRP)_{1–36}$ on cAMP responses and PTHR internalization in cultured cells. The $PTH_{1–34}$–PTHR complex was rapidly internalized into endosomes and was not associated with desensitization of the cAMP response. By contrast, $PTHRP_{1–36}$ actions were reversible and limited to the plasma membrane. These results may explain how PTH and PTHRP can signal through one receptor and trigger different durations of cAMP responses.