Metalloproteinase inhibitors

Metalloproteinases are secreted or cell surface proteases that degrade or proteolytically activate other cellular molecules and components of the extracellular matrix (ECM). These enzymes are important for control of cell-cell and cell-ECM interactions during cell migration, differentiation and proliferation and are regulated by a number of inhibitors. In a Commentary on p. 3719, Gillian Murphy and co-workers review our understanding of these inhibitors, which include the tissue inhibitors of metalloproteinases (TIMPs), TIMP-like molecules such as netrins, α2 macroglobulin, and novel proteins such as RECK. TIMPs are ~21-kDa proteins that inhibit all known matrix metalloproteinases (MMPs). Not all of their effects appear to be due to inhibition of MMPs, however. TIMP2, for example, has mitogenic effects on erythroid precursor cells, acting through receptors linked to G-proteins and cyclic AMP signalling. Similarly, the biological activities of RECK during angiogenesis probably extend beyond its ability to inhibit MMP-2, MMP-9 and MT1-MMP, and α2 macroglobulin might well do more than just inhibit endoproteinases. Murphy and co-workers suggest that only when these additional activities are fully understood will we be able to exploit the therapeutic potential of metalloproteinase inhibitors.

Integrins and apoptosis

Binding of cell surface integrins to the extracellular matrix (ECM) stimulates a variety of intracellular signalling pathways. Integrin signalling can activate the PI 3-kinase and MAP kinase pathways, for example, and thereby induce cells to proliferate; however, it can also stimulate apoptosis. In a Commentary on p. 3729, Dwayne Stepnick and David Cheresh discuss the different ways in which integrins tip the balance between cell survival and cell death. The simplest case is perhaps anokiasis, in which the absence of a survival signal provided by integrin anchorage leads to apoptosis. Integrin signalling can also induce resistance to apoptotic stimuli directly – through pathways that target the Bcl-2 and IAP families of apoptosis regulators and death effector domain (DED) proteins. Alternatively, it can promote ‘integrin-mediated death’, and this appears to depend on the context of the binding event (i.e. whether the integrin ligand is soluble or substrate immobilized). Integrins can thus act as biosensors that respond to specific ECM compositions by generating death or survival signals appropriate for maintenance of tissue architecture and remodelling during development and repair processes.

Intracellular calcium pathways

Calcium plays a crucial role in cell signalling. But it is sometimes hard to keep track of the numerous channels and pumps that allow this particular cation to enter and exit cells and move between the cytosol and intracellular stores – let alone the wide variety of different extracellular signals that can modulate cellular calcium levels. In Cell Science at a Glance (see p. 3715 and the accompanying poster), Martha Nowisky and Andrew Thomas make this task a little easier, surveying all the key players involved in calcium signalling and the mechanisms that preserve calcium homeostasis.

In this issue

Metalloproteinase inhibitors

Integrins and apoptosis

Intracellular calcium pathways

In the next issue of JCS

Sticky Wicket

Q&A offense and defense. Caveman

Cell Science at a Glance

Fibronectin, R. Pankov and K. M. Yamada

Commentaries

pre-mRNA processing. K. M. Neugebauer

Protein kinase CK2. L. A. Pinna

Research Articles

Binding of PKB to periplakin. A. P. J. van den Heuvel et al.

NCS-1 and PI4KII interaction and membrane translocation. E. Taverna et al.

A nucleolar targeting sequence of WRN. C. von Kobbe and V. A. Bohr

NSF in Paramecium. R. Kissmehl et al.

PAK4 in MDCK cells. C. M. Wells et al.

β-endorphin and uPAR expression. F. Besta et al.

Conventional kinesin in regulated exocytosis in β-cells. A. Varadi et al.

Molecular assembly of nematocysts. U. Engel et al.

Bgs1p localization during the life cycle. J. C. G. Cortés et al.

Replication patterns in normal and cancer cells. D. S. Dimitrova and R. Berezney

Astrin is an essential protein. J. Gruber et al.

A role for yeast Vps34 PI 3-kinase in cellular trafficking. P. Burda et al.