PDE5 says NO to cGMP

A short burst of nitric oxide (NO) is remembered by a phosphodiesterase long after NO levels decline, according to results on page 719 by Mullershausen et al. The memory of this enzyme, PDE5, may be responsible for the tolerance that patients develop to nitrovasodilators like nitroglycerin. Nitrovasodilators are NO-releasing compounds that are used to treat coronary heart disease. NO increases cellular cGMP levels, which lowers blood pressure by both relaxing blood vessels and inhibiting platelet aggregation. But platelets rapidly decrease NO-induced cGMP and thus become desensitized to later NO exposure. Circumstantial evidence suggests that the cGMP is degraded upon phosphorylation of the phosphodiesterase PDE5 by a cGMP-dependent kinase. The new article describes a more direct route of cGMP self-limitation.

As expected, NO-induced PDE5 phosphorylation required cGMP increases and the cGMP-dependent kinase cGKI. Yet phosphorylation was not necessary for PDE5 activation by cGMP, as shown using cGKI-deficient mice. Instead, cGMP was sufficient to activate PDE5. Others recently showed that cGMP binds to and activates PDE5. This interaction probably provides the direct mechanism for NO-induced PDE5 activation. Low concentrations of cGMP, however, stimulated only phosphorylated PDE5, suggesting that the modification may increase cGMP affinity.

A small, transient NO stimulus dampened subsequent cGMP production in response to NO for 1 h later, at which time PDE5 was still active. Inhibition of this active PDE5 may be necessary to achieve lasting nitrovasodilator therapy.

A protease inhibitor unsticks cells

PAI-1 is unique among protease inhibitors because it binds to the matrix protein vitronectin (VN). PAI-1 binding blocks VN’s binding site for the cell surface receptor uPAR and for integrin family members. Czekay et al. (page 781) now show that PAI-1 is also able to detach cells through a less direct approach.

Unlike the direct competition method, PAI-1 also disrupted integrin-mediated adhesion without ever contacting VN. Instead, PAI-1 bound to another uPAR ligand, the protease uPA. Binding of uPA to uPAR causes integrin recruitment into complexes with uPA and uPAR. PAI-1 disrupted adhesion by inactivating these complexes and triggering their endocytosis. Endocytosis required the low density lipoprotein receptor-related protein, but how PAI-1 triggers integrin inactivation has yet to be determined.

Integrins interact with other matrix molecules in addition to VN. So far, the authors have shown that PAI-1 also detaches cells from fibronectin and collagen, again by promoting integrin endocytosis. In each case, cells expressing high levels of uPAR were more susceptible to PAI-1–induced detachment, because more of their surface integrins were complexed with uPAR. This association could explain why a high level of PAI-1 indicates a poor prognosis for many metastatic cancers—unusual for a protease inhibitor, since proteases normally promote cell invasion.

Ran sticks a GEF to chromatin

Gradients of the small GTPase Ran are important throughout the cell cycle. High nuclear RanGTP concentrations in interphase cells regulate nuclear transport. During mitosis, chromosome-localized RanGTP releases spindle assembly factors from sequestration by importins. On page 635, Li et al. demonstrate that RanGTP accumulates at chromosomes because the complex of Ran and its guanine nucleotide exchange factor (GEF) binds strongly to chromatin.

GTP-bound Ran is produced by the GEF RCC1, which binds only weakly to histones. Using a GFP-tagged version, the authors show that RCC1 is highly mobile and exchanges rapidly between free and chromatin-bound states. As RCC1 has strong GEF activity in the presence or absence of chromatin, the authors were interested in determining how RanGTP production is limited to chromosomes. They found that Ran-bound RCC1 had a stronger chromosome association. Locking RCC1 to chromosomes because the complex of Ran and its guanine nucleotide exchange factor (GEF) binds strongly to chromatin in vitro. Only nucleotide exchange, which displaces RCC1 from Ran, released the GEF and RanGTP from chromosomes.

The increased affinity of the complex for chromosomes can be explained by its binding geometry. RCC1 binds histones H2A and H2B, whereas Ran binds weakly to histones H3 and H4. The complex is therefore well suited to bind to nucleosome octamers. Thus, exploiting the geometry of nucleosomes is a simple way to couple GTP exchange to chromatin-bound Ran.