activation loop from the large lobe butts into the other end. The resulting position of helix C forces a residue that is probably critical for kinase activity — Glu 310 — away from the active site. Activation of the kinase (for example, by dephosphorylation of the tail), would presumably lead to the sequential dissociation of the SH2 and SH3 domains from their intramolecular ligands, removing one constraint on helix C. Furthermore, autophosphorylation of Tyr 416 in the activation loop would result in reorganization of this sequence, thereby lifting the second constraint.

Why adopt this remarkably complex way of regulating Src-family kinases? Xu *et al.*¹ and Sicheri *et al.*² have shown that when Tyr 527 is phosphorylated, not only is the kinase domain repressed, but the SH2 and SH3 domains are tied up in intramolecular interactions, such that they cannot associate with exogenous ligands and disturb SH2/SH3-regulated signalling events. Does this mean that c-Src is activated simply by dephosphorylation of Tyr 527? Although this is likely to be the key regulatory switch, things may be more complicated. For example, the intramolecular interactions in which the SH2 and SH3 domains are engaged are probably very weak, and more potent exogenous ligands for either domain may compete for binding, thereby disrupting the inactive structure.

Moarefi *et al.*³ have addressed this issue by showing that a phosphopeptide that binds with high affinity to the Hck SH2 domain stimulates kinase activity (as has previously been shown for c-Src¹⁴), presumably by competing the SH2 domain away from phosphorylated Tyr 527. This may be of physiological relevance, as autophosphorylation of the β platelet-derived growth-factor receptor creates a binding site for the c-Src SH2 domain¹⁵, which could elevate the kinase activity by displacing the SH2 domain.

Moarefi *et al.* also show that the HIV Nef protein — a potent ligand for the Hck SH3 domain — stimulates the activity of Hck that is phosphorylated at Tyr 527, and even increases the activity of the dephosphorylated protein. So the SH3 domain could exert a residual repressive activity in the absence of the intramolecular phosphotyrosine-SH2 interaction. Several substrates for Src-family kinases have proline-rich motifs onto which the SH3 domain can dock, and this binding may tether the substrate to the kinase and concomitantly stimulate the kinase activity. Phosphorylation of a single tyrosine site in the substrate would then promote intermolecular SH2-binding, and hence a strong bidentate association between the enzyme and the substrate, which could stimulate processive phosphorylation of the substrate. This may be especially pertinent for substrates such as p130^{cas} and its relative Sin/Efs, which are phosphorylated at many sites by

Src-family kinases, and which once phosphorylated act as docking proteins for other signalling proteins with SH2 domains^{16,17}.

Modular interactions of the sort shown for Src kinases are also important for the Tec family of intracellular tyrosine kinases, among which the Btk kinase (Fig. 1) is well known for its involvement in human X-linked agammaglobulinaemia¹⁸. Btk has an amino-terminal pleckstrin homology (PH) domain that binds specifically to phosphatidylinositol-3,4,5-trisphosphate¹⁹, and may be involved in recruitment to the membrane. The PH domain is followed by a proline-rich sequence (the Tec homology, or TH, region), and by SH3, SH2 and kinase domains. Unlike the Src-family kinases, members of the Tec family are not regulated by carboxy-terminal phosphorylation: instead, the SH3 domain apparently undergoes an intramolecular interaction with the TH region, which could restrict access of the SH3 domain to potential substrates²⁰. Phosphorylation of a tyrosine residue within the SH3 domain²¹ may disrupt the intramolecular SH3-TH interaction, thereby liberating the SH3 domain to engage kinase substrates.

Tec-family kinases therefore depend on modular interactions for their regulation and target recognition — but in a rather different way from the Src-family kinases. Taken with the results of Xu *et al.*¹, Sicheri *et al.*² and Moarefi *et al.*³, these findings underscore the extraordinary versatility of protein modules such as SH2, SH3 and PH domains; however, there is clearly still much to be discovered about the structures, biochemistry and biological functions of Src and Tec kinases. □

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Daedalus

A problem dissolved

In popular medical demonology, cholesterol has a prominent place. It gets itself deposited in our arteries, often as local and dangerous constrictions.

Many epidemiologists blame components of our diet. Cholesterol itself is an obvious suspect; but since the body makes it as required and disposes of any surplus, it cannot be the whole story. Another suspect, alcohol, attracts both blame and praise. Countries such as France combine a high alcohol intake with relatively little heart disease. Can the antioxidants in red wine, or even alcohol itself, have some protective effect? Daedalus now points out the obvious protective mechanism. Cholesterol is slightly soluble in alcohol.

So, says Daedalus, a bloodstream loaded with alcohol should slowly dissolve cholesterol deposits, or should fail to lay them down in the first place. For best effect, the subject should drink steadily all the time, maintaining an even level of alcohol in his blood. This 'French' style of alcoholism contrasts strongly with the 'English' style of occasional wild alcoholic binges interspersed with periods of remorseful sobriety. While DREADCO's epidemiologists study the cardiological records of various styles of alcoholic, the firm's chemists are seeking a better inebriating solvent than alcohol.

One obvious alternative is ether. It dissolves cholesterol and its esters much better than alcohol, and is usefully soluble in blood. It is not very toxic (it is a traditional anaesthetic), and even causes its own brand of drunkenness, the nineteenth century 'ether frolic'. Many people might love to be kept slightly blotto on ether for several weeks, while the stuff strips the cholesterol from their arterial constrictions, and carries it to the liver for disposal — or simply redeposits it more evenly around the whole vascular system, without dangerous concentrations.

Another alternative is methyl *t*-butyl ether, MTBE. Though better known as an antiknock additive for petrol, it has in fact been used to dissolve cholesterol gall stones *in vivo*. It is not miscible with blood, and would have to be injected in emulsion form. MTBE might function as a sort of vascular flushing oil, stripping the deposits from the patient's arteries and holding them in suspension. Some sort of kidney-machine could filter off the suspended cholesterol and return the purified blood to the patient. Most people should prefer the occasional discomfort of flushing out to the grimly permanent rigours of a healthy lifestyle.

David Jones