selects peptides with the sequence EEEYMMMM. To a first approximation, then, receptors appear to have a preference for phosphorylating sites that will bind group III SH2 domains.

The SH2 domains of intracellular PTKs generally recognize phosphotyrosine followed in the +1 and +2 positions by an acidic residue, with a hydrophobic residue at +3 (a feature of group I SH2 domains)⁶. Remarkably, the Fps/Fes, Src and Abl PTKs preferentially phosphorylate peptides that are well suited to bind their own

FIG. 2 Complementary functions of the kinase and SH2 domains of intracellular PTKs. The catalytic domains of kinases such as Src, Abl and Fps/Fes phosphorylate tyrosine motifs that subsequently bind with high affinity to the adjacent SH2 domain. In some cases, this may allow for repeated phosphorylation of the same molecule at several sites, as proposed for p130^{cas} phosphorylated by Abl^{1,14}.

SH2 domains. These results indicate that the SH2 domains of intracellular kinases may be involved in substrate recognition, as originally suggested, but in the sense that they bind proteins after phosphorylation by the neighbouring kinase domain. This might protect these substrates from dephosphorylation, hold them at a specific subcellular location, or allow for repeated phosphorylation of the same substrate, once it is tethered to the SH2 domain (Fig. 2). A good candidate for such processive phosphorylation is the p130^{cas} protein¹², which was originally identified by its ability to bind the SH2 domains of the Abl and Src kinases, and through its association with the Crk adaptor protein¹³. This protein has multiple Ile/Val-Tyr-X-X-Pro motifs, which in principle would be preferred substrates for the Abl kinase, and once phosphorylated should bind the Abl SH2 domain.

This raises the possibility that, following phosphorylation by the Abl kinase, p130^{cas} is captured by the Abl SH2 domain and is held in place for subsequent rounds of phosphorylation. There is evidence for this model, in that strong p130^{cas} phosphorylation by the Abl kinase seems to be dependent on the Abl SH2 domain¹⁴; in addition, the Crk adaptor protein, which binds to a proline-rich site in the Abl tail through its SH3 domain, contributes to processive p130^{cas} phosphorylation by

supplying, in *trans*, another SH2 domain to which p130^{cas} can bind. Like Abl SH2, the Crk SH2 domain favours pTyr-X-X-Pro sites. This suggests a novel role for SH2/SH3 adaptor proteins in modifying the specificity of intracellular PTKs.

Songyang *et al.* have an additional piece of data to support their cause. Homology modelling suggests that the +1 residue of a peptide substrate fits into a pocket lined by a methionine in most receptor PTKs, possibly accounting for their preference for hydrophobic amino acids at this position. Cytoplasmic PTKs, which select acidic residues at this position, have a threonine in place of the methionine. A substitution of the methionine in the presumptive +1-binding pocket of the Ret PTK for a threonine is associated with the human familial cancer multiple endocrine neoplasia type 2B (ref. 15), suggesting that this cancer might result from an alteration in Ret substrate specificity to resemble that of cytoplasmic PTKs^{1,16}.

These results are useful for thinking about signalling by PTKs. In particular, the substrate specificity of PTK kinase domains matches rather well with the binding specificity of SH2 domains, indicating that tyrosine kinases and SH2 domains have co-evolved, the former to phosphorylate sites that will be bound by the latter. The techniques pioneered by Songyang *et al.* will probably lead to a tremendous expansion in our knowledge of the substrate specificity of protein kinases. With increasing numbers of protein-kinase structures being solved, their recognition of substrates can be set on a structural footing. Similarly, as genomic and complementary DNA sequences become available, it becomes a simple job to search the database for likely protein kinase substrates. Ultimately, it may be possible to predict the substrate specificity of a protein kinase, and identify potential substrates, entirely on the basis of sequence information. □

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DAEDALUS

Stifled sound

THESE days we are surrounded by unwanted sound. Traffic roars on every road, Muzak pullulates in every public space, burglar and car alarms wail neglected in ever more urban areas, and personal radios and tape-players are everywhere. So Daedalus is inventing a super sound absorber, using the well-known aerogel process. This swells a solid to a tenuous gel in liquid carbon dioxide, then takes the system above its critical point and bleeds off the CO₂ as gas. The resulting expanded solid can be almost as light as air. DREADCO's chemists are now turning rubbers and elastomers into light and tenuous aerogels. Their low density gives them an acoustic impedance well matched to air, while their high elastic damping absorbs any sound traversing them.

DREADCO's Silentgel will be ideal for earplugs, cavity-wall fillings, acoustic tiles and sonic absorbers of all kinds. But Daedalus also sees the need for a selective sound absorber, to cut out maddening background noises but let through the loud direct sounds we want or need to hear. For this purpose, he is marketing Silentgel in the subtle form of a 100-nm coating on a harder backing. This thickness matches the typical vibrational displacement of a soft sound. Impinging on the thin coating, such a sound loses almost all its energy in compressing and dilating the flaccid film. By contrast a loud sound, with a displacement of 1 µm or more, is hardly absorbed at all. It flattens the coating completely, or dilates it fully, with 10 per cent of its cycle or less. The rest is reflected or transmitted without loss.

Sonic Subtractor film will clarify our sound-sabotaged lives. It will cut out the general sonic sludge, but let the useful information through. In the form of earplug diaphragms, it will present you with clear and distinct sounds only: close speech intended for your ears, or music that you have actually chosen to listen to. Similarly, in wallpaper form it will wonderfully sharpen a lecture theatre or restaurant. It will reflect the main speech, or conversation within a nearby group, but will absorb the distracting background hubbub.

Subtractor film will have a special effect on sound of intermediate loudness. It will damp the low-amplitude parts of its cycle, but pass its peaks unattenuated. The resulting 'crossover distortion' is sometimes produced by cheap amplifiers. It is extraordinarily annoying. So a background sound which slowly gains intensity will be very obvious by its sudden grating harshness. A waiter surreptitiously turning up the Muzak will be immediately detected. David Jones