

in that the peptide binds in a shallow groove on the surface of the β -barrel (5). These three examples show just how versatile a protein fold can be.

Different domains for more or less the same function

So far, the discussion has centred on proteins of similar structure but different function. The other important feature regarding evolution of proteins from domain building blocks is the apparent ability to evolve completely different structures to perform very similar biological roles. From left to right, the three examples shown in the top row of **Fig. 2** describe phosphotyrosine recognition, phosphatidylinositol binding and proline-rich peptide binding, respectively. In the bottom row of the figure, there are three protein domains whose functions match the proteins shown directly above them, and yet it is immediately obvious that they bear no structural relationship at all.

The PTB and Src homology 2 (SH2) domains both bind phosphorylated tyrosine side chains but do so very differently. In the case of the SH2 domain, the phosphate group is buried in a deep pocket interacting with positively charged arginine residues and the amino acids following the modified tyrosine residue dictate specificity for a particular domain-phosphopeptide interaction. In PTB domains the interaction site is very much on the surface of the protein, with the residues N-terminal to the phosphorylated tyrosine providing ligand-specificity. The phosphate group is not deeply buried, partly explaining why phosphorylation of much shorter side chains such as serine can be tolerated in some examples. The deep binding pocket found in the SH2 domain excludes this possibility, restricting the domain to phosphotyrosine ligands only.

The Phox homology (Px) domain is a newly described structure that is largely α -helical and binds the phosphorylated inositol head groups of phospholipids in a pocket formed at the apex of a number of helices. This is

very different to the PH domains and the combination of the two provides a way of dealing with the complicated mixtures of multiply phosphorylated membrane lipids on the cytoplasmic surface of cells.

The well-studied SH3 domain has now been joined by a number of domains capable of binding proline-rich peptide sequences including EVH1, WW domains and the small cytoskeletal protein profilin. In each of these cases the binding surface is rich in aromatic residues (Phe, Trp and Tyr) with adjacent charged residues providing specificity for the particular ligand. Interestingly, some of the WW domains only bind proline-rich peptides that contain a phosphorylated serine residue, clearly explaining how such interactions would be controlled within the cell.

With the enormous quantity of sequence data now available from the various genome projects, it is anticipated that fingerprints for many novel domains will be uncovered. As their 3D structures are characterised, we can look forward to many delightful surprises of conserved structures or functions. Nature has clearly learned that once you're on a good thing . . . stick to it!

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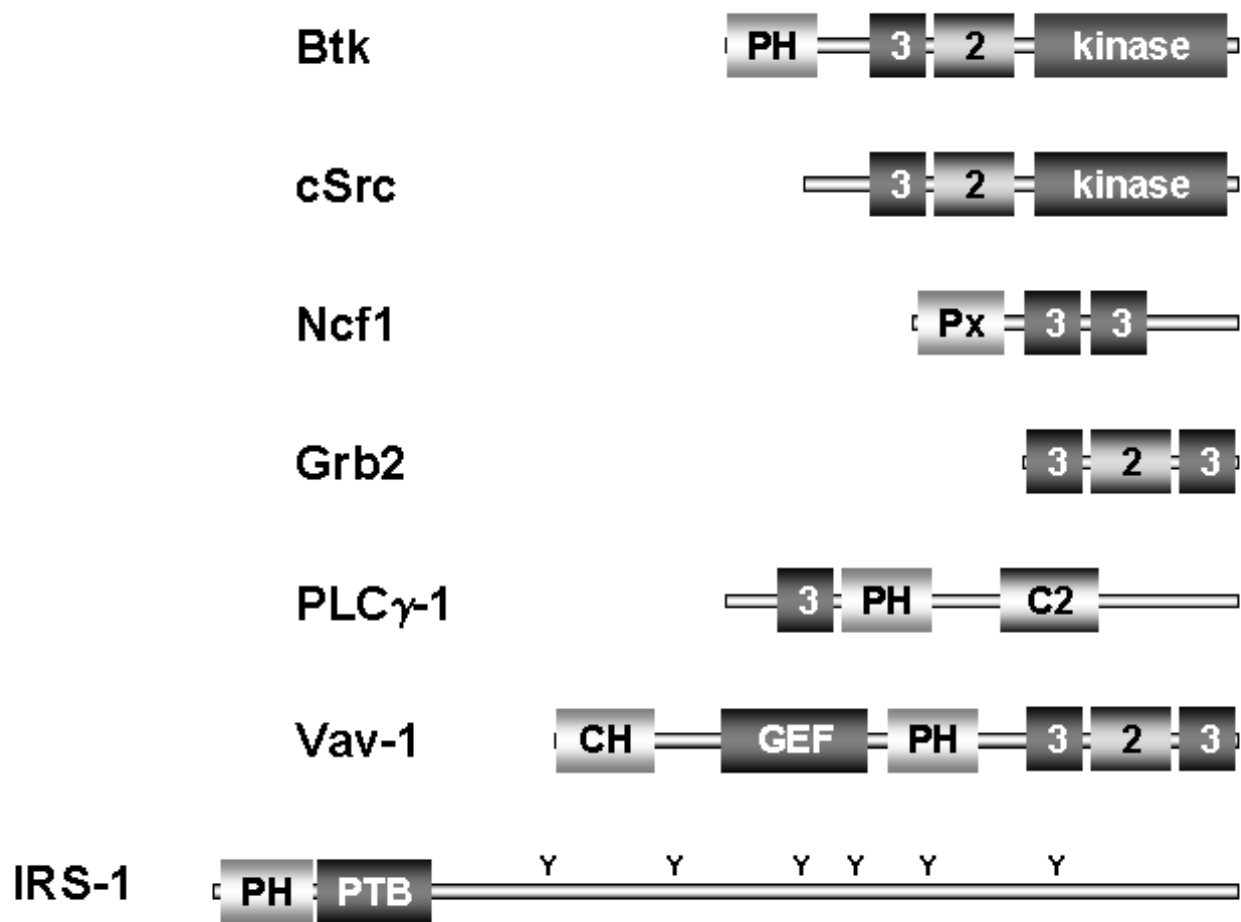


Fig. 1

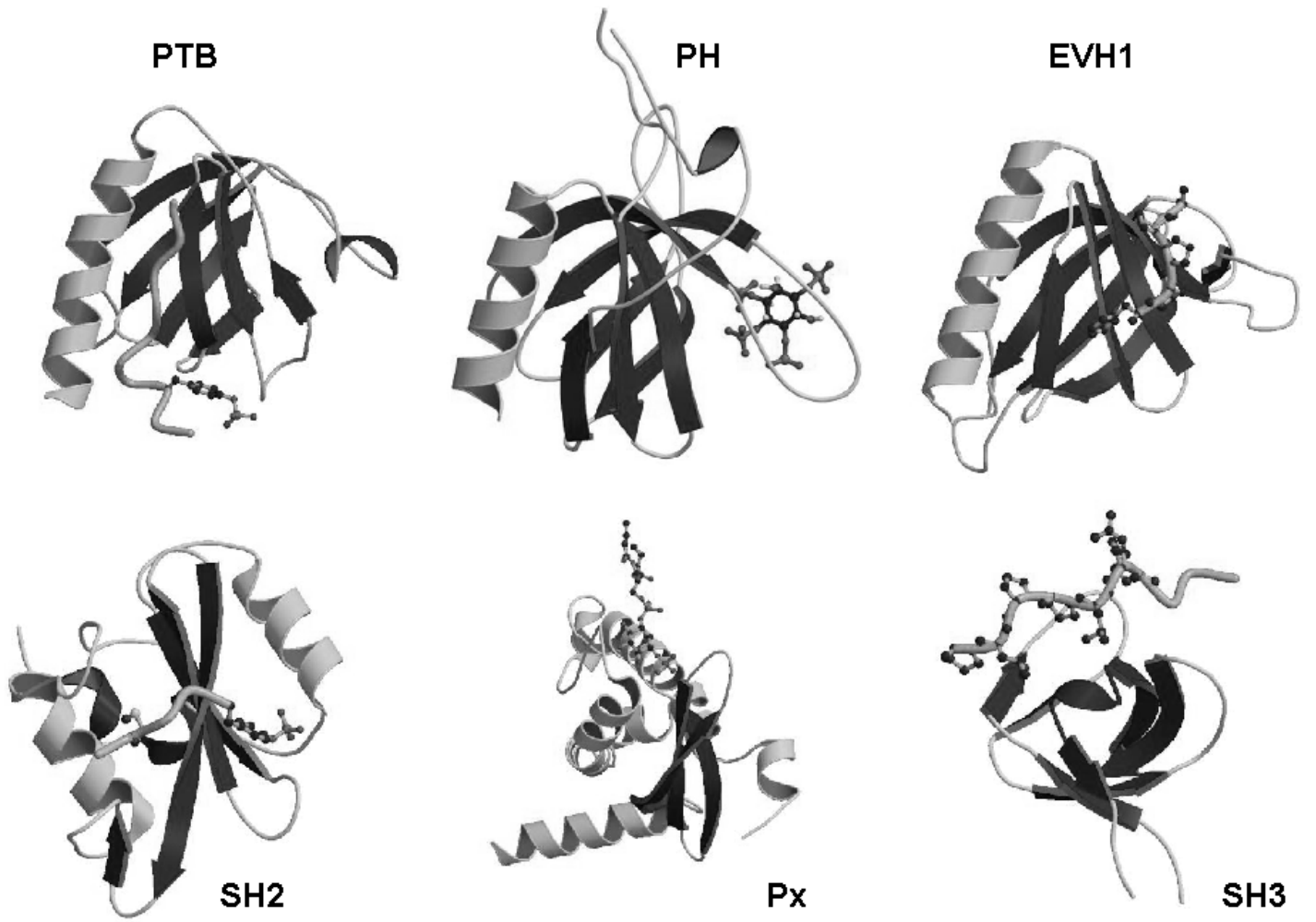


Fig. 2