An SH2–SH3 domain hybrid

SIR — We report a striking similarity between the three-dimensional structures of the *src* homology 2 domain (SH2)[1] and domain II of the repressor of the *Escherichia coli* biotin biosynthetic operon (BirA)[2]. We used a protein-structure comparison algorithm[3] to compare the X-ray structure of the chicken *src* SH2 domain to a non-redundant subset of the Brookhaven protein databank[4], and found that BirA and SH2 share 51 equivalent Cα atoms that superimpose with an r.m.s. deviation of 2.13 Å. Four strands of a central β-sheet and two helices packing on either side of this sheet lie in equivalent positions in the structure. BirA has an insertion of 49 residues relative to SH2 between the third and fourth strands. The insertion includes an α- helix and three β-strands which extend the SH2 domain sheet (see figure). An analysis of other SH2 sequences[5] shows that one, avian tensin, has an insertion of 22 residues at the same location. This suggests that the insertion in the tensin SH2 domain may extend the β-sheet in a similar fashion to BirA.

Noble *et al.*[6] have drawn attention to the similarity of domain III of BirA to the SH3 domain structure. Taken together with our findings, this shows that BirA comprises an SH2–SH3 domain hybrid with an amino-terminal helix–turn–helix domain. There are many examples of SH2- and SH3-containing proteins[7], but no structure of an SH2–SH3 complex has yet been determined. BirA thus provides a possible structural model for the SH2–SH3 complex.

Both SH2 and BirA bind phosphate. SH2 binds phosphotyrosine-containing peptides, whereas BirA catalyses the formation of biotinyl-5′-adenylate from biotin and ATP. The interaction between phosphotyrosine and SH2 is well understood[1,8,9], but for BirA structural evidence is available only for the biotin–enzyme complex (not for the ATP–enzyme complex). Biotin binds to BirA on domain II on one face of the central β-sheet, and near the amino terminus of the first helix. Surprisingly, this is nearly identical to the binding site for phosphotyrosine on SH2. Although BirA does not seem to have any of the residues known to interact with phosphate within the SH2 domain, the ATP-binding site is thought to be in a disordered loop region containing arginine and glycine near the FLVRESET phosphate-binding region on SH2. The structural similarity suggests that BirA undergoes a conformational rearrangement similar to that of SH2 on binding to phosphate.

No prokaryotic counterpart to the SH2 and SH3 domains has previously been identified. Although the functions are different, the structural similarity, similar binding site and coincidence of both SH2 and SH3 domains in a single molecule described here, suggests that BirA may share a common ancestor with SH2 and SH3 domains. It is tempting to suggest such an evolutionary link between the SH2 and SH3 domains, which are involved in various stages of the cytoplasmic signalling cascade[10], and a transcriptional regulator, which has ultimate control over gene expression.

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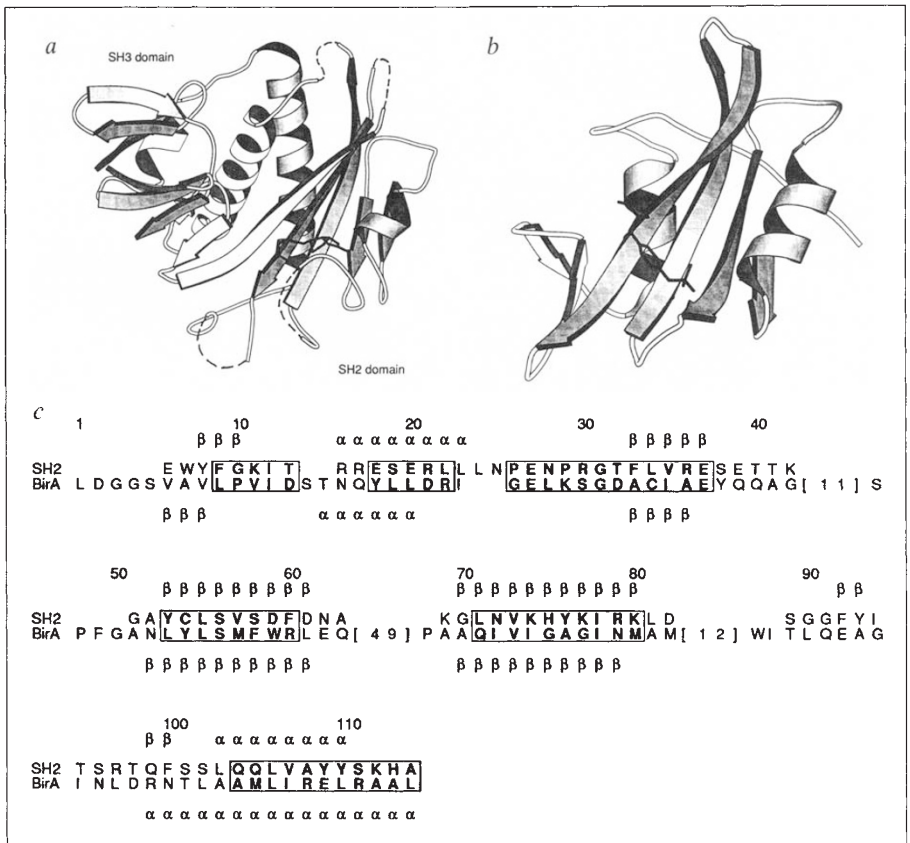

a, Molscript[11] drawing of the three-dimensional structure of BirA[2], excluding the amino-terminal helix–turn–helix domain. The shaded regions show the SH2-like domain II, and the SH3-like domain III. The unshaded region corresponds to the 49 residue insertion relative to the *src* SH2 domain. Dashed lines in BirA, regions for which no electron density is seen. The experimentally determined location of bound biotinylated lysine is shown in stick form. *b*, The structure of *src* SH2 domain[1] in the same orientation as *a*, showing the experimentally determined location of bound phosphotyrosine. Shading highlights the regions similar to BirA. *c*, Structure-derived sequence alignment of SH2 and the BirA equivalent domain[3]. Boxed bold-face regions show structural equivalences. Secondary structure assignments were made using the program DSSP[12]: α, α-helix; β, β-strand. Missing residues in BirA at alignment positions 43 and 83 are due to poor electron density in these regions within the X-ray structure. The proposed phosphate binding loop is at position 43 and contains the sequence GRGRRG. 49 residues were removed from BirA at position 65 for clarity. Only 8 of the 51 structurally equivalent residues are identical.

1. Waksman, G. *et al. Nature* **358**, 646–653 (1992).
2. Wilson, K. P. *et al. Proc. natn. Acad. Sci. U.S.A.* **89**, 9257–9261 (1992).
3. Russell, R. B. & Barton, G. J. *Proteins: Structure, Function and Genetics* **14**, 309–323 (1992).
4. Bernstein, F. C. *et al. J. molec. Biol.* **112**, 535–542 (1977).
5. Russell, R. B. *et al. FEBS Lett.* **304**, 15–20 (1992).
6. Noble, M. E. M. *et al. EMBO J.* **12**, 2617–2624 (1993).
7. Heldin, C. *Trends biochem. Sci.* **16**, 450–452 (1991).
8. Eck, M. J. *et al. Nature* **362**, 87–91 (1993).
9. Waksman, G., Shoelson, S. E., Pant, N., Cowburn, D. & Kuriyan, J. *Cell* **72**, 779–790 (1993).
10. McCormick, F. *Nature* **363**, 15–16 (1993).
11. Kraulis, P. J. *J. Appl. Cryst.* **24**, 946–950 (1991).
12. Kabsch, W. & Sander, C. *Biopolymers* **22**, 2577–2637 (1983).

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