carbonyl group of the seryl-hydroxamate-AMP in SerRS) occupy a similar position between strands 6 and 7 in both enzymes, being very similarly oriented and within 4 Å of each other in this superposition.

There is no significant sequence similarity between the catalytic domains of the two proteins and thus it is impossible to prove any indisputable divergent evolutionary relationship between them. It is therefore entirely possible that no such relationship exists. The similarity reported here may be due to convergent evolution towards a common stable fold, or towards a structure dictated by a particular functional requirement, as for example in the α/β-barrel proteins analysed by Chothia[19]. However, it has been noted by Matthews and Rossmann[20] and by Sali and Blundell[21] that in the evolution of proteins, tertiary structure would be expected to be conserved more than amino acid sequence. Such an argument would support the likelihood of divergence from a common ancestor for the BirA and SerRS catalytic domains. This possiblity is strengthened by the long-established functional similarities between BirA and the tRNA synthetases[2] and by the fact that the strong structural resemblance that we have demonstrated involves a complex and unusual 3-D fold, and a very similar location of the active sites in the two proteins.

From this viewpoint it is possible that the striking structural similarity we have found is indicative of a remote divergent evolutionary relationship between the family of class II tRNA synthetases and biotin synthetase. The situation becomes more intriguing when one takes into account the similarity, mentioned above, between part of the biotin synthetase catalytic domain and an SH2 domain[10]. Taken together with the similarity between the BirA C-terminal domain[9] and the SH3 fold, this finding prompts the speculation that BirA may represent a structural 'missing link' between the SH2/SH3 domain proteins and the class II tRNA synthetases. Whether this is the case or not, the similarity between the catlytic domains of BirA and SerRS lends support to Eisenberg's early hypothesis[2]. But what of Berg's still earlier one?[1]. At present, the 3-D structure of acyl-coA synthetase has not been solved; when it has been, it will be interesting to see where it fits in the scheme of things.

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In reply:

Evolutionary implications

The fact that BirA and Class II aminoacyl-tRNA synthetases have a topologically equivalent fold for their catalytic domains is of great interest from an evolutionary point of view. Unlike Class I synthetases–which have the widespread, dinucleotide binding (Rossmann) fold for their catalytic domain, class II synthetases have hitherto appeared to have a completely unique ATP–binding domain (apart from the possible case of asparagine synthetase, as mentioned above). If the catalytic domains of BirA and Class II synthetases indeed have a common ancestor (although convergent evolution cannot be excluded), this leads to the speculation that this common ancestor was an ATP–binding domain that could activate small cofactors. Specialization to amino acids as substrates and the acquistion of 3′ end RNA binding and aminoacylation activity would have led to the first Class II synthetase. More specialised tRNA recognition domians, especially for the anticodon, would have been added later and are indeed much more structurally variable amongst Class II synthetases than the catalytic domain. This scenario of evolution of aminoacyl-tRNA synthetases is consistent with previous views (for example refs 23,24), but begs the question: if there were proteins before aminoacyl-tRNA synthetases, how were those proteins made?

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1. Berg P. *J. biol. Chem.* **222**, 991–1013 (1956).
2. Eisenberg, M.A. *Adv. Enzymol.* **38**, 317–372 (1973)
3. Grindley, H.M., Artymiuk, P.J., Rice D.W. & Willett P. *J. molec. Biol.* **229** , 707–721 (1993).
4. Wilson, K.P., Shewchuk, L.M., Brennan, R.G., Otsuka, A.J. & Matthews, B.W. *Proc. natn. Acad. Sci. U.S.A.* **89**, 9257–9261 (1992).
5. Cusack, S., Berthet-Colominas, C., Härtlein, M., Nassar, N. & Lebermann, R. *Nature*, **347**, 249–256 (1990).
6. Eriani, G., Delarue, M., Poch, O., Gangloff, J. & Moras, D. *Nature* **347**, 203–206 (1990).
7. Moras D. *Trends biochem Sci* **17**, 159–164 (1992).
8. Cronan, J.E. *Cell* **58**, 427–429 (1989).
9. Noble, M.E.M., Musacchio, A., Saraste, M., Courtneidge, S.A. & Wierenga, R. *EMBO J.* **12**, 2617–2624 (1993).
10. Russell R.B. & Barton G.J. *Nature* **364**, 765 (1993).
11. Brick, P. & Blow D.M. *J. molec. Biol.* **194**, 287–297 (1987).
12. Biou, V., Yaremchuk, A., Tukalo, M. & Cusack, S. *Science* **263**, 1404–1410 (1994).
13. Belrhali, H. *et al. Science* **263**, 1432–1436 (1994).
14. Gatti, D.L & Tzagoloff, A. *J. molec. Biol.* **218**, 557–568 (1991).
15. Ruff, M., *et al. Science* **252**, 1682–1689 (1991).
16. Bernstein, F.C., *et al. J. molec. Biol.*, **112**, 535–542 (1977).
17. Artymiuk, P.J., Grindley, H.M., Park, J.E., Rice, D.W. & Willett, P., *FEBS Letts.* **303**, 48–52 (1992).
18. Artymiuk, P.J., Grindley, H.M.. Kumar, K., Rice, D.W. & Willett, P. *FEBS Letts.* **324**, 15–21 (1993).
19. Chothia, C. *Nature* **333**, 598–599 (1988).
20. Matthews, B.W. & Rossmann, M.G., *Meth Enzymol.* **115**, 397–420 (1985).
21. Sali, A. & Blundell, T.L. *J. molec. Biol.* **212**, 403–428 (1990)
22. Kraulis, P.J. *J. appl. Crystallogr.* **24**, 946–950 (1991).
23. Schimel, P., Geige, R., Moras, D. & Yokoyama, S. *Proc. natn. Acad. Sci. U.S.A.* **90**, 8763–8768 (1993).
24. Cusack, S. *Biochimie* **75**, 1077–1081 (1993).