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Cysteine or serine proteinase?

SIR—We have noticed an apparent discrepancy in the sequence alignment published in a recent scientific correspondence by Higgins *et al.*[1] in reporting the possible identification of a new cysteine proteinase in *Plasmodium falciparum*. The cysteine at amino-acid position 22 of papain was incorrectly labelled as the active site cysteine. This cysteine has been shown to form an essential disulphide bridge in papain, whereas Cys 25 of papain has been shown by crystallographic and chemical studies to be the catalytic cysteine[2,3]. Cys 25 forms an ion pair with the imidizole of His 159, with Asn 175 completing the essential catalytic triad of papain. These residues are conserved in cysteine proteinases of highly divergent organisms.

It is interesting that the amino-acid residue which is in the correct catalytic site of the *P. falciparum* protein is a serine. All known serine proteinases contain a catalytic triad (composed of histidine, aspartic acid and the catalytic serine) that has convergent active-site geometry with the cysteine proteinases. The presence of a serine at the catalytic site of the *P. falciparum* antigen indicates that this protein is actually a serine proteinase with a cysteine proteinase conformation, a structure that is similar to a class of cysteine trypsin-like proteinases found in viruses[4].

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SIR—Higgins *et al.*[1] showed that the 111K antigen of *Plasmodium falciparum* has significant similarity to cysteine proteinases. We wish to point out that the cysteine labelled as the putative active-site residue is in fact involved in a disulphide bridge in papain, actinidin and probably other cysteine proteinases[5]. The gene sequence for the 111K antigen predicts a serine at the active-site position (residue 588; see refs 6 and 7). Although it has yet to be confirmed that the protein itself contains an active-site serine, as post-transcriptional modification could result in the generation of a cysteine[8], the presence of a serine would have functional and evolutionary implications. The serine could have arisen from a cysteine by a single base mutation (TGC → TCC), with a subsequent change to the present serine codon, TCA. This would support the suggestion that proteinases with serine at the active site may have evolved from cysteine proteinases[9]. Could this malarial protein represent an intermediate between these two classes of proteinase?

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1. Higgins, D.G., McConnell, D.J. & Sharp, P.M. *Nature* **340**, 604 (1989).
2. Drenth, J., Jansonius, J.N., Koekoek, R., & Wolthers, B.G. *Adv. Protein Chem.* **25**, 79–115 (1971).
3. Husain, S.S. & Lowe, G. *Biochem. J.* **108**, 855 (1968).
4. Bazan, J.F. & Fletterick, R.J. *Proc. natn. Acad. Sci. U.S.A.* **85**, 7872–7876 (1988).
5. Kamphuis, I.G., Drenth, J. & Baker, E.N. *J. Molec. Biol.* **182**, 317–329 (1985).
6. Knapp, B. Hundt, E., Nau, U. & Kupper, H.A. *Molec. Biochem. Parasitol.* **32**, 73–84 (1989).
7. Li, W-B., Bzik, D.J., Horli, T. & Inselburg, J. *Molec. Biochem. Parasitol.* **33**, 13–26 (1989).
8. Goldfarb, P.S. *Nature* **336**, 429 (1988).
9. Brenner, S. *Nature* **334**, 528–530 (1988).