In a variant of this model, we might imagine that the interaction of membrane-bound ARF–GTP with GGAs induces a conformational change in GGAs, which facilitates specific recognition between the sorting signal and the VHS domain of GGAs, as well as that between the clathrin box of GGAs and the N-terminal domain of clathrin. In this case, ARF–GTP would be the 'activator' of GGAs . In either case, the challenge now is to figure out how the GGA proteins manage to coordinate all these interactions that seem to occur simultaneously in time and space, to do it in such a way that no error in the recruitment to the correct membrane is made, and to ensure that proper sorting and budding is achieved. The linear domain organization of GGAs provides a wonderful opportunity to help tease apart the process from a structural point of view.

Tomas Kirchhausen is in the Department of Cell Biology, Harvard Medical School and The Center for Blood Research, Boston, Massachusetts 02115, USA. email: kirchhausen@crystal.harvard.edu

1. Kirchhausen, T. *Annu. Rev. Biochem.* **69**, 699–727 (2000).
2. Dell'Angelica, E.C. *et al. J. Cell Biol.* **149**, 81–93 (2000).
3. Hirst, J. *et al. J. Cell Biol.* **149**, 67–79 (2000).
4. Boman, A.L., Zhang, C.J., Zhu, X.J. & Kahn, R.A. *Mol. Biol. Cell* **11**, 1241–1255 (2000).
5. Poussu, A., Lohi, O. & Lehto, V.P. *J. Biol. Chem.* **275**, 7176–7183 (2000).
6. Lohi, O. & Lehto, V.P. *FEBS Lett.* **440**, 255–257 (1998).
7. Puertollano, R., Aguilar, R.C., Gorshkova, I., Crouch, R.J. & Bonifacino, J.S. *Science* **292**, 1712–1716 (2001).
8. Zhu, Y.X., Doray, B., Poussu, A., Lehto, V.P. & Kornfeld, S. *Science* **292**, 1716–1718 (2001).
9. Takatsu, H., Katoh, Y., Shiba, Y. & Nakayama, K. *J. Biol. Chem.* **276**, 28541–28545 (2001).
10. Nielsen, M.S. *et al. EMBO J.* **20**, 2180–2190 (2001).
11. Misra, S., Puertollano, R., Kato, Y., Bonifacino, J.S. & Hurley, J.H. *Nature*, **415**, 933–937 (2002).
12. Shiba, T. *et al. Nature*, **415**, 937–941 (2002).
13. Ter Haar, E., Harrison, S.C. & Kirchhausen, T. *Proc. Natl. Acad. Sci. USA* **97**, 1096–1100 (2000).
14. Owen, D.J. *et al. Cell* **97**, 805–815 (1999).
15. Rapoport, I., Chen, Y.C., Cupers, P., Shoelson, S.E. & Kirchhausen, T. *EMBO J.* **17**, 2148–2155 (1998).
16. Gatto, G.J., Geisbrecht, B.V., Gould, S.J. & Berg, J.M. *Nature Struct. Biol.* **7**, 1091–1095 (2000).
17. Scheufler, C. *et al. Cell* **101**, 199–210 (2000).
18. Kirchhausen, T. *Annu. Rev. Cell Dev. Biol.* **15**, 705–732 (1999).
19. Kirchhausen, T. *Nature Rev. Mol. Cell Biol.* **1**, 187–198 (2000).

Does Dengue virus fuse using β-barrels?

Dengue virus is transmitted to humans by mosquitoes, and there are more than 50 million infections each year. Typical symptoms include severe joint pain and fever, but serious complications such as hemorrhagic fever and Dengue shock syndrome sometimes occur following infection. Fortunately, less than 0.1% of Dengue infections are fatal, but it is still a major concern for health officials around the world.

The structure of Dengue virus at 24 Å resolution is now available and has been analyzed in the context of previous crystallographic work on one viral protein (Kuhn, R.J. *et al. Cell* **108**, 717–725; 2002). Kuhn and coworkers embarked on this study to understand how the virus is organized and to obtain clues about how it enters host cells. While much is known about how some viruses (such as HIV) fuse to target membranes, the mechanism of Dengue virus fusion is thought to be quite different.

Kuhn and colleagues used cryoelectron microscopy to solve the structure of one Dengue strain at neutral pH, the pH at which viral particles do not fuse to membranes. The structure that emerges resembles an onion, with five distinct sheets visible in the electron density — two outer protein shells (dark and light blue), a lipid bilayer (green), a nucleocapsid shell (orange), and finally, the RNA genome (red) packaged in the center of the virus. They focus attention on the structure of the outermost shell, the layer that first contacts target membranes.

E glycoprotein is the viral component that mediates fusion to membranes. The crystallographic structure of an E glycoprotein from a related virus is known, and it contains a large amount of β-structure. Kuhn and colleagues fit this atomic structure into the electron density of the outermost shell of Dengue virus, revealing a closely packed array of E glycoproteins. They propose that, upon exposure to low pH, parts of the E glycoproteins change conformation and form closed β-barrels.

In other proteins, such as porins, β-barrels allow membrane spanning. By the same token, β-barrels on the surface of Dengue virus might be capable of inserting into target membranes, thereby promoting viral fusion. This proposed mechanism is distinct from the fusion system used by HIV, which relies instead upon a spring-like α-helical coiled coil.

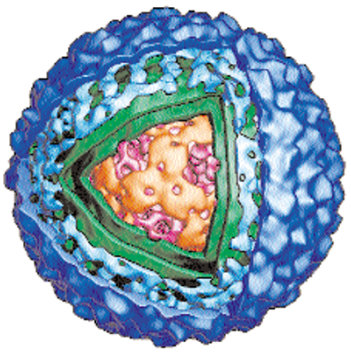

Figure kindly provided by Wei Zhang

Dengue virus is spreading, and there is no vaccine. It used to be confined primarily to Southeast Asia but is now common in South and Central America. Moreover, within the last six months, outbreaks have occurred in both Brazil and Hawaii. Now more is learned about the potentially novel fusion apparatus of this virus, perhaps new drugs to hamper it could be developed — just as fusion inhibitors that target the coiled coil mechanism of HIV are now being tested.

Tracy Smith