Tick-borne encephalitis virus reveals its access code

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Fritz et al. have identified an amino acid switch that flaviviruses flip to gain access to cells. Flaviviruses such as tick-borne encephalitis virus (TBEV), yellow fever, and dengue are dangerous human pathogens. These membrane-encircled viruses enter cells by being gobbled up into endosomes and fusing their membrane with that of the endosome.

Fusion is triggered by the endosome's acidic environment. Low pH prompts the aptly named fusion protein, on the virus's outer membrane, to change shape and grab hold of the endosome membrane, bringing the two membranes together. In their search for possible pH sensors, researchers have focused on five highly conserved histidine residues in the flavivirus fusion protein. The chemical properties of histidines make them prime candidates—they switch from uncharged to having a double positive charge upon acidification of their environment, such as that in endosomes.

Fritz et al. replaced each of the five histidines of the TBEV fusion protein with alternative residues and observed the virus's fusion ability. Given the conservation of the five histidines, the team was surprised, that mutation of one of the histidines, His323, was sufficient to completely abolish fusion. Individual mutation of three of the others had no effect on fusion whatsoever, and mutation of the fourth led to an untestable ill-formed fusion protein.

The team went on to show that mutation of the crucial His323 interfered with the pH-induced shape change of the fusion protein.

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