very interesting, he says. But p53 does a lot of other things, he adds. 'I would like to consider that perhaps there are other functions of p53 that are playing a role here as well,' he said. 'I would like to see them address these other pathways.'

Scrable has already begun to look at how the inability to regenerate is affecting different systems in the body, starting with the brain. 'It looks like p53 really is a central regulator of lifespan, but it's going to take us some time to figure out what that means exactly if we go system by system in the animal,' she said. 'We certainly have unexpected results.'

Reference

1 Maier, B. *et al.* (2004) Modulation of mammalian life span by the short isoform of p53. *Genes Dev.* 18, 306–319

Unfolding targets for dengue fever

Sadaf Shadan, BMN News

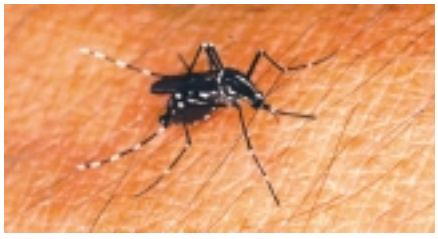
Recent structural data show conformational changes in envelope proteins of the dengue virus during fusion with the host membrane, providing important clues for the development of therapeutic drugs against a number of viral diseases, report researchers.

Fusion proteins

Specific proteins on the membrane of enveloped viruses are categorized into two classes. Class I fusion proteins are found on the surface of HIV and influenza virus among others. These differ structurally from class II proteins, which are found on the membrane of viruses responsible for diseases such dengue fever, hepatitis C, West Nile and yellow fever.

The structural differences between proteins from the two classes have led to the assumption that they also differ mechanistically. The available information on the fusion mechanism of class I proteins with the host plasma membrane has contributed to the development of existing therapies against HIV. Now, ultrastructural analysis of glycoprotein E on the surface of dengue virus provides data that suggest parallel entry mechanisms for viruses with class I and class II fusion proteins [1].

Researchers led by Stephen Harrison, a principal investigator at Harvard Medical School (http://www.hms.harvard.edu), used the crystal structure of the glycoprotein E to study its insertion into the host membrane. From the data obtained using this high-resolution approach, they propose a mechanism for the entry of dengue virus into the host cell.



Dengue virus vector *Aedes albopictus* feeding on a human host. DC/PHIL/James Gathany

Pore formation

According to the model, binding of glycoprotein E to receptors on the host-cell surface and/or exposure to low pH lead to orientational rearrangements in the three domains of this protein. Consequently, a trimer of exposed fusion peptides forms and directly binds to the host-cell membrane. The protein, which is now attached to both viral and host-cell membranes, undergoes further conformational changes pulling the two membranes close together. The resulting membrane fusion leads to the formation of pores and thus the entry of viral genetic material.

In addition to elucidating the entry mechanism of viruses with class II proteins, these data are important for designing drugs against the wide range of diseases caused by this group of viruses, claim the researchers. Dengue fever alone infects 50–100 million people worldwide each year. The most severe form of the disease is dengue hemorrhagic fever, which affects 0.5 million individuals and is life threatening.

Treatment approaches

These latest data highlight several possible approaches to the treatment of dengue fever, says lead author Harrison. 'There would be several targets: a protease, a helicase, and a polymerase,' he said. 'We plan to work on two categories of potential fusion inhibitors. But I believe the first therapeutics are more likely to be enzyme inhibitors.'

Highlighting the broader significance of this study, Harrison added, 'A more important therapeutic target is hepatitis C virus, which may have a similar structure for its fusion protein. We hope to pursue this problem, based on our success with dengue.'

Reference

1 Modis, Y. et al. (2004) Structure of the dengue virus envelope protein after membrane fusion. *Nature* 427, 313–319

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