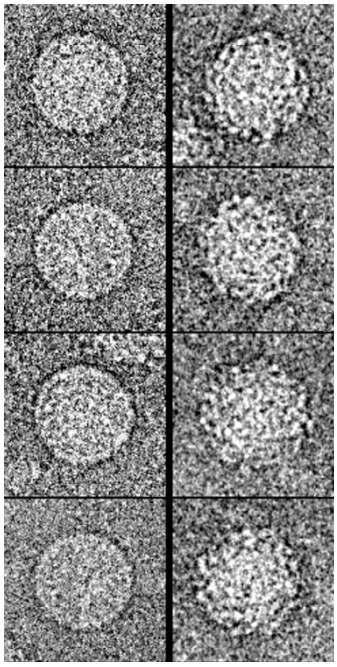
Dengue likes it hot



Dengue fever is a mosquito-borne viral infection that affects over 300 million people each year. The dengue viral particle undergoes conformational changes during its maturation process, going from a 'spiky' immature form to a 'smooth' mature virion, whose cryo-EM structure is available; crystal structures of the envelope glycoprotein E have also been solved. One puzzling observation was that several epitopes recognized by neutralizing monoclonal antibodies are not exposed in the smooth, mature viral particle at room temperature (20 °C). Now work from Rossmann and colleagues may help solve this mystery. The authors incubated mature dengue virus particles at 37 °C, the temperature inside the human host, and then examined them by using cryo-EM. In contrast to the smooth particles seen at room temperature, the viral particles had a 'bumpy' appearance at 37 °C. These were different from the spiky immature form, which was the same at 20 or 37 °C. The transition from smooth to bumpy mature particles occurs between 31 and 35 °C, and this conformational change is irreversible. The authors determined the three-dimensional structure of the bumpy particle and fitted in the crystal structure of the glycoprotein-E dimer, which revealed a different arrangement of the dimers as compared to the smooth form. Notably, the bumpy structure is similar to a fusogenic intermediate form of dengue virus that was proposed over a decade ago. This indicates that the bumpy mature dengue virus is the predominant form in the human body and the one that actually infects human cells. Supporting this notion, the bumpy particles showed higher infectivity than did the smooth particles in a cell culture assay. This hypothesis needs to be further investigated, but a change to a 'ready-to-infect' form of dengue virus, triggered by the temperature shift upon entry into the human host, would constitute a remarkable example of host adaptation and have clear implications for vaccine development. (*Proc. Natl. Acad. Sci. USA* http://dx.doi.org/10.1073/pnas.1304300110, published online 8 April 2013) *IC*

Helicase disc breaks

DNA replication requires a dedicated enzyme to unwind the duplex ahead of the DNA polymerase traveling in its wake. In bacteria, this role is served by DnaB, a hexameric ring helicase that is positioned at replication origins by the helicase loader DnaC, an AAA+ ATPase that works with initiation-factor DnaA to form a prereplication complex. The closed-ring architecture of DnaB prompts the question of how DnaC loads it onto the template, whether by promoting ring assembly around the DNA or by opening the ring to thread the template through. The structure of the *Escherichia coli* DnaB–DnaC complex recently reported by Berger and colleagues provides clear evidence for the latter. A combination of EM and SAXS shows that, whereas the apo form of DnaB is a closed ring, the DnaB–DnaC complex forms a spiral structure with a cracked ring and a central channel that is potentially accessible to DNA. Six DnaC subunits engage and open the DnaB hexamer, which is positioned such that its N-terminal domains form a collar around one end of the channel while its motor domains contact the DnaC N termini. Intriguingly, the AAA+ domains of DnaC are arranged in a spiral configuration characteristic of polymerase sliding-clamp loaders, which perform an analogous ring-opening function through their ATPase domains. However, in this case, DnaC's AAA+ domain is dispensable for DNA loading and unwinding *in vitro*, which suggests that DnaB remodeling involves distinct ATP-independent interactions with the DnaC N terminus to form the loading complex. ATP hydrolysis may instead help destabilize the DnaB collar and enhance transition to a translocation-competent conformation. Future determination of DNA-bound complex structures will help to define the role of the DnaB collar in regulating helicase activity and reveal potential similarities with the eukaryotic hexameric helicase, MCM2-7. (*Cell* **153**, 438–448, 2013) *BM*

A histone mutation in cancer

Missense mutations K27M and G34R/V in the human genes encoding histones H3.3 and H3.1 are present in the majority of pediatric gliomas. Allis and coworkers now have shown that histones extracted from diffuse intrinsic pontine gliomas containing the K27M mutation have significantly lower H3K27me3 levels and that H3K27M transgenes also cause a global decrease in H3K27me3. Although cells carrying the H3.3G34R/V mutation did not exhibit a global reduction in H3K36me3, the authors found reduced H3K36me2 and H3K36me3 levels on H3.3G34R/V-containing nucleosomes. Moreover, H3.3G34R/V-containing nucleosomes were methylated to a lower extent by recombinant SET2 *in vitro*. Whereas H3K27me3 peptides allosterically stimulated PRC2 methyltransferase activity on nucleosome substrates, H3K27M peptides inhibited PRC2 activity on nucleosomes. This dose-dependent inhibition was specific to K27M, as other substitutions did not affect the methylation efficiency. Synthesized photoactivatable H3K27M peptides could be cross-linked to the SET domain–containing EZH2 catalytic subunit but not to other PRC2 subunits, which suggests that K27M peptides inhibit PRC2 through interaction with the EZH2 active site. Other SET-domain methyltransferases were found to be similarly sensitive to methionine substitution at their cognate methylated lysines (H3K9 and H3K36). The authors propose that aberrant epigenetic silencing by the H3K27M gain-of-function mutation through inhibition of PRC2 activity may promote gliomagenesis, and the current work further suggests that other K-to-M histone mutations may be linked to disease. (*Science* http://dx.doi.org/10.1126/science.1232245, published online 28 March 2013) *AH*

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