KEMIJSKI INŠTITUT

Predavanje / Lecture

Open sesame! Activation and inactivation of picornaviral entry studied using integrated structural biology

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Velika predavalnica, 1. nadstropje / Great Lecture Hall, 1st floor

Viruses belonging to the genus Enterovirus are widely spread major pathogens. Their capsids are icosahedrally-symmetric with 60 copies of VP 1 - 4 forming asymmetric subunits. VP 1-3 are structurally similar resembling a ß-sheet jelly roll and form a protective shell on the surface while VP4 interacts with the genome on the inside. At the base of each VP1 is a hydrophobic pocket which in most enteroviruses houses a lipid factor. Cellular triggers can cause expulsion of the lipid from the hydrophobic pocket resulting in expansion of the virus into a porous form through which RNA, VP4 and the N-termini of VP1 can exit. Preventing genome release and stabilizing the capsid are potential antiviral approaches. We studied coxsackievirus A9 using several techniques including asymmetric flow field flow fractionation, thermostability assays, cryogenic electron microscopy and image reconstruction methods to resolve several of these metastable structures to atomic resolution. Localized reconstruction and focused classification were extensively utilized to successfully separate particle heterogeneity in the dataset. We found that mimicking endosomal ion conditions and treatment with fatty-acid free bovine serum albumin could both trigger coxsackievirus A9 A-particle formation. Further we studied the binding of small molecules that inhibited virus infection, carrying out structure activity relationship analyses on molecules binding to the VP1 hydrophobic pocket and to a second interprotomer pocket that we discovered initially in coxsackievirus B3. These findings contribute to our understanding of the role of the host in viral genome release, the process of viral entry and support efforts towards antiviral drug design and vaccine development.

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Vljudno vabljeni / Kindly invited