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Evolutionary links among viruses of different categories revealed by dsRNA virus capsid structures

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This talk will describe recent X-ray structures of double-stranded RNA (dsRNA) virus capsids, and discuss the possible evolutionary links among them and with viruses with a positive sense, single-stranded RNA (+sRNA) genome. An important feature of dsRNA virus capsids is formation of totally non-equivalent contacts between capsid proteins (CPs) during particle assembly. In particular, they present of a typical icosahedral structure composed of 120 copies of CP, which results in totally different environments for the two subunits of the icosahedral asymmetric unit. A notable exemption is constituted by the birnaviruses, which have a capsid of triangulation T=13, a symmetry that is also present in the second layer of the complex dsRNA viruses of the Reoviridae family (for instance, rotaviruses). Unlike rotaviruses, birnaviruses share many similarities with +sRNA viruses, and lack the characteristic layer made by 120 copies of CP observed in the others. This structure establishes clear links between coat proteins of viruses belonging to two radically different categories. Recent studies of a smaller version of birnaviruses, the “picobirnaviruses”, revealed that they are actually unrelated to birnaviruses, and do display a 120-subunit capsid architecture typical of dsRNA viruses. Interestingly, this structure appears very similar to that of dsRNA viruses of the Partitiviridae family, with a virion formed by 60 symmetric CP dimers. Together, these results provide important insights into the multiple functions of dsRNA virus capsids, and reveal unanticipated structural relationships among icosahedral viruses. They suggest a picture for a possible evolutionary pathway leading to emergence of the complex Reoviridae by combination of genomic segments from simpler viruses.

Keywords: double-stranded RNA viruses, capsid structures, icosahedral symmetry

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Structure of the trimeric, prefusion Ebola virus GP complexed with an antibody from a human survivor

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Ebola virus (EBOV) belongs to the family filoviridae and causes a severe hemorrhagic fever with 50-90% human mortality. EBOV entry requires the surface glycoprotein, GP, to initiate attachment and fusion of viral and host membranes. Here we report the crystal structure, at 3.4 Å resolution, of a trimeric and pre-fusion conformation of GP (GP1+GP2) in complex with a neutralizing antibody fragment, KZ52, derived from a human survivor of the 1995 Kikwit outbreak. The construct crystallized contains all domains required for attachment, fusion and entry, and leads to productive cellular infection when pseudotyped onto vesicular stomatitis virus. In the structure, three GP1 viral attachment subunits assemble to form a chalice, cradled in a pedestal comprised of the GP2 fusion subunits, while a novel glycan cap and projected mucin-like domain restricts access to the conserved receptor-binding site sequestered in the chalice bowl. The glycocalyx surrounding EBOV GP is likely central to immune evasion and explains why patients that survive have low to insignificant neutralizing antibody titres. The KZ52 antibody recognizes a protein epitope at the chalice base where it clamps several regions of the pre-fusion GP2 to the N terminus of GP1 and precludes rearrangements required for fusion. This structure now provides a template for unraveling the mechanism of Ebola virus GP-mediated fusion and for future immunotherapeutic development. This work is supported by NIH grants AI067927 and NIH-AI053423 to EOS, and NIH-AI048053 to DRB, a Canadian Institutes of Health Research Fellowship to JEL, and a Career Award from the Burroughs Wellcome Fund to EOS.

Keywords: viral glycoprotein, Ebola virus, neutralizing antibody

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(Re-)emerging viral diseases: How can structural biology support preparedness and response?

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The number of viral outbreaks has been increasing dramatically recently. In the past twelve years, the world has seen at least one major outbreak of either a new virus or a new variant of a known virus per year. Incidentally, almost all of these outbreaks were caused by RNA rather than DNA viruses. Immediate containment of viral outbreaks depends on quarantine and antiviral drugs. Unfortunately, for most known viral diseases of humans, and let alone for newly emerging ones, no drug treatment is available. We believe that in view of this scenario, it is necessary to develop lead compounds with activity against all major families of viruses, both those that infect humans and those that so far have been restricted to animals but may cross the species-barrier by zoonotic transition. Ultimately, we should aim at discovering antiviral compounds with a relatively broad specifity, which may be active against a range of new viruses should they emerge. We believe in the merits of structure-based approaches to discover new compounds with activity against RNA viruses. Methods applied include virtual screening, fragment ligation, and structure-guided medicinal chemistry. We focus on components of the viral replicase complexes as targets for antiviral compounds, and in particular on the proteases that play essential roles in the viral life cycle. As examples, structural studies and inhibitor discovery will be described for proteases of coronaviruses including the SARS virus, norovirus, and coxsackievirus as well as other enteroviruses. Some of the latter have entered tests of in-vivo activity in a mouse model.

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