Structural insights into the $2A_2$ protein from Duck Hepatitis A virus

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Picornaviridae are a large and growing family of biomedically and agriculturally important viruses. Family members cause a wide range of diseases such as poliomyelitis, Foot-and-mouth disease, and hepatitis A, but also less severe diseases such as the common cold. Picornaviruses are non-enveloped, ss (+) RNA viruses, which means that their genome can act as a mRNA upon entry into the host cell cytoplasm. The genome size ranges between 7-10 kb and contains one open reading frame that is translated into one polyprotein, which is processed into mature proteins by viral, chymotrypsin-like proteases. The picornavirus genome is restricted in size and mainly encodes for proteins that are essential for capsid formation (P1 region) and virus replication (P2-P3 regions). The 2A region, however, is one of the most divergent parts of the genome, and the number and function of the 2A proteins varies between different picornaviruses (1). The avian picornaviruses are of particular interest, as many of them have acquired several types of 2A proteins, with Duck egg reducing syndrome virus (DERSV) currently holding the record with 7 consecutive 2A proteins, of 3 different types ($2A^{NPGP}$, $2A^{GTPase}$, $2A^{H/NC}$). Several of these proteins are thought to be host-derived, but their role(s) in the viral replication cycle is mostly unknown. Our aim is to characterize these probably host derived 2A proteins and elucidate how they contribute to viral replication & modulation of host (innate)immune responses. One of the avian viruses we are studying is the Duck Hepatitis A virus type1 (DHAV1), which causes severe hepatitis and has a mortality rate of 95 % in ducklings under the age of six weeks, causing severe economic losses for the farmers. DHAV1 has three different types of 2A proteins, at the moment the project focuses on the second non-structural 2A protein ($2A_2$) which is a GTPase. This protein is reported to interact with Mitochondrial Anti-Viral Signaling protein (MAVS) and to induce pyroptosis, an inflammatory cell death pathway, in duck embryos, by activating gasdermin E via caspase-3 mediated cleavage. (2) The Alphafold 3 model of DHAV1-$2A_2$ is structurally related to the human GTPase Immunity Associated Protein (GIMAP) family as well as a family of plant GTPases (Toc proteins). We can now present an X-ray crystallography structure of the apo state of the $2A_2$ protein from DHAV1, which reveals that it indeed shares many features with the GIMAP and Toc proteins. Further biophysical and biochemical characterization is needed to unravel the function(s) of these 2A proteins in the viral life cycle and help us answer the question why these viruses have acquired these proteins.

References

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