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Protein biogenesis in the *Picornaviridae*: Virus-encoded proteinases, ribosome 'skipping', alternative initiation and programmed ribosomal frame-shifting

The genome structure of viruses within the Picornavirus family is similar to cellular mRNAs: +v sense RNA genomes comprising a long 5' non-coding region (NCR), a single open reading frame (ORF; ~2,300 aa), a short 3'-NCR with a poly(A) tail, although the 5' cap structure is quite different. When introduced into the cytoplasm, the virus RNA can function directly as a messenger RNA. The challenge faced by these viruses is, however, the need to generate a multiplicity of different proteins (capsid, RNA replication proteins) from this single ORF. All picornaviruses encode a proteinase ($3C^{pro}$) which 'processes' the polyprotein into mature products by a combination of a single, co-translational, intramolecular cleavage (in *cis*) and multiple post-translational intermolecular cleavages (in *trans*). Some picornaviruses have acquired a second proteinase (aphthoviruses – L^{pro}; enteroviruses – $2A^{pro}$) which perform a single co-translational cleavage in *cis*, but then go onto cleave cellular proteins involved in the cap-dependent translation of host-cell mRNAs and proteins involved in interferon production in response to infection. The 2A region of aphtho- and many other *Picornavirus* genera (unlike enteroviruses not a proteinase) may either be a short oligopeptide sequence, or, a larger protein that mediates a translational 'recoding event termed 'ribosome skipping' at the C-terminus of 2A such that translation stops (releasing the nascent protein) then recommences translation of the down-stream replication protein sequences: an apparent 'cleavage', but in actuality a discontinuity in the polypeptide backbone. It is now known that this form of control over protein biogenesis is used by other types of RNA virus and some cellular genes. Uniquely within the picornaviruses, Theiler's murine encephalomyelitis virus (TMEV; genus cardiovirus) encodes an overlapping, alternative ORF within the leader, or L protein, alternative initiation producing the L* protein which plays an important role in the establishment of persistent CNS infections by TMEV. Recently it has been shown that some picornaviruses also use programmed ribosomal frame-shifting shortly after the ribosome skipping event to (translationally) down-regulate the production of replication proteins at later stages of the infectious cycle. Furthermore, this frame-shifting does not rely solely on an RNA secondary structure, but is directed by protein 2A. In conclusion, the picornaviruses have evolved a range of different mechanisms to control their protein biogenesis: not at the level of RNA transcription, but by co- and post-translational events alone.

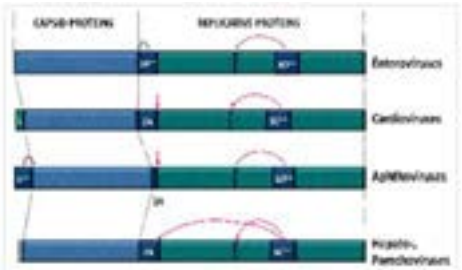

Figure 1: Picornavirus polyproteins. The polyprotein domain comprising the capsid proteins is co-translationally separated from those comprising the replication proteins by a 2A proteinase ($2A^{pro}$) in the enteroviruses (proteinase cleavages shown by curved arrows), 'ribosome skipping' (cardio-, aphthoviruses plus other genera: shown as vertical arrows) or the 3C proteinase ($3C^{pro}$) for e.g. hepato-, parechoviruses. A further co-translational cleavage occurs to separate the major domains of the replication proteins – in all cases mediated by $3C^{pro}$.

Biography

Martin D Ryan has cloned and sequenced the genome of Enterovirus Type 70 as a part of his PhD research work. He then went on to work on FMDV polyprotein processing at the Pirbright Institute. After moving to University of St. Andrews in 1994 he continued this work, focusing upon the mechanism of FMDV 2A-mediated 'cleavage' – showing it was not a proteolytic element, but mediated a novel form of translational recoding – 'ribosome skipping'. Other lines of research led to the development of 2A as a protein co-expression system – now used very widely in biotechnology and biomedicine. In 2017, he was awarded the Unilever Colworth Prize for his work on 2A. More recently, his laboratory has been working on FMDV RNA replication using a replicon system encoding fluorescent proteins such that FMDV RNA replication can be monitored by live-cell imaging.

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