

RNA virus replication, transcription and recombination

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In October of 2009 a group of researchers with a common interest in RNA virus reproduction met to present and discuss their recent findings on molecular mechanisms related to viral genome replication at a Cantoblanco Workshop on Biology: "Replication and Recombination of RNA Virus Genomes" in Madrid, Spain (co-organized by Luis Enjuanes, Ben Berkhout and K. Andrew White). The exciting discussions during the meeting provided the inspiration for this Special Focus Issue of *RNA Biology* on **RNA virus replication, transcription and recombination** that offers a forum to expand on some of the topics presented at the Cantoblanco Workshop.

The genomes of RNA viruses play the obvious critical role of genetic repository for the production of viral proteins. However, these genomes also carry out multiple functions during virus reproduction in addition to serving as mRNAs for translation. Such additional duties include the critical roles as template for genome replication and transcription of viral subgenomic (sg) mRNAs, as well as participation in other diverse functions, e.g. virion assembly. Accordingly, viral genomes contain numerous regulatory RNA elements that promote, regulate and coordinate these diverse molecular processes. As such, viral RNA genomes can be considered dynamic molecules that adopt different local and global RNA structures in a spatially and temporally regulated manner. Indeed, for some RNA viruses, the viral genome can be considered to be a conductor that orchestrates multiple viral processes in the infected cell. The central role played by viral RNA genomes is frequently executed by viral or host cell proteins that interact with these genomes, but the functional partners may also be other RNA molecules, e.g. the cellular tRNA primer that initiates reverse transcription of the retroviral RNA genome. The protein partners come in a variety of forms and provide critical enzymatic or structural functions needed for successful virus reproduction. Together, the protein and RNA factors interact with cellular pathways to allow viruses to successfully hijack the host cell machinery for virus production. The reviews in this special issue describe some of the fascinating roles played by dynamic RNA genomes of different classes of RNA viruses.

Virus RNA genome replication. The replication of a viral genome is a fundamental step in the virus life cycle. For both plus- and minus-strand RNA viruses, this process proceeds

through a complementary RNA strand intermediate, whereas for retroviruses, the intermediate is DNA. In this special issue, the important role of various viral and host proteins in viral RNA genome replication are described in review articles that span these three types of RNA-based viruses. Denison et al.¹ and Ulferts and Ziebuhr² present an update on the role of virally-encoded ribonucleases in nidovirus genome replication and the potential role for this class of protein in providing RNA proof-reading activity for these large RNA genomes. Resa-Infante et al.³ describe the structure and function of the ribonucleoprotein complex responsible for replication of the influenza virus genome, while Li and Nagy⁴ provide a comprehensive overview of host RNA-binding proteins and their roles in plus-strand RNA virus replication. Several reviews of diverse viral systems illustrate the central role played by RNA structure in genome replication. Iglesias and Garmarnik⁵ relay how the equilibrium between linear and pseudo-circular forms of the Dengue virus genome is important for optimal viral multiplication. Berkhout⁶ describes how both local and long-range RNA-RNA interactions in the HIV-1 genome are important for replication and the amazing ability of this virus to rapidly adapt when such interactions are perturbed. Mechanistic aspects of the minus-strand transfer step during HIV-1 reverse transcription and the RNA and protein co-factors involved are reviewed by Piekna-Przybylska and Bambara⁷, while the fascinating replication of viroids and similar non-coding RNA replicons that involves rolling circle intermediates are described by Flores et al.⁸. The articles on genome replication are completed by the contribution of Alvisi et al.,⁹ who describe the important role of lipids in the RNA genome replication of hepatitis C virus.

Subgenomic mRNA transcription. One common gene expression strategy used by many plus-strand RNA viruses with polycistronic genomes is to produce subgenomic (sg) mRNA molecules. These shorter than genome length viral messages allow for the controlled expression of a subset of viral genes. Two different mechanisms for generating sg mRNAs are reviewed in this issue. Sola et al.¹⁰ describe the discontinuous mechanism and associated regulatory schemes used by coronaviruses, while Jiwan and White¹¹ review viral examples in the family Tomoviridae that use a premature termination mechanism for sg mRNA transcription.

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Viral RNA genome recombination. The ability to genetically recombine provides many viruses with the ability to rapidly adapt to new environmental situations, e.g. infection of a new host cell type or the initiation of an antiviral drug therapy. In most cases, this event is mediated by an actively copying viral polymerase “hopping” from one template to another and such occurrences have been reported for both plus-strand RNA viruses and retroviruses. The role of recombination in pestiviruses and its ability to influence pathogenicity is recounted by Becher and Tautz.¹² Simon-Loriere et al.¹³ discuss the highly recombinogenic nature of HIV-1 that is driven by the unique property of retroviruses to package two copies of the RNA genome. More specifically, they argue for an important role of template RNA secondary structure in mediating recombination and consequently virus evolution.

We hope that readers will enjoy this compilation of RNA virus reviews that provide different perspectives on various steps of virus reproduction that involve dynamic viral RNA sequences and structures that function along with viral and host factors.

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Co-Editors

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