REPLICATION, VIRUS-HOST INTERACTION AND PROTECTION IN CORONAVIRUSES

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Summary

The coronaviruses are single-stranded positive-sense RNA viruses with genomes of around 30 kb, responsible for infections of the respiratory and enteric mucosal tissues. Coronaviruses have high impact on animal and human health. Our group is interested in the molecular basis of replication and transcription, assembly, and virus-host interaction using transmissible gastroenteritis coronavirus (TGEV) and the severe and acute respiratory syndrome virus (SARS-CoV) as models. The information derived from these studies is being applied to the engineering of coronavirus based vectors.

Both virus replication and transcription, and virus-host interactions are mediated by the binding of virus RNA motifs to virus and host proteins and by protein-to-protein interactions. We have postulated that coronavirus transcription and replication involve 5' and 3' genome ends interaction, and the potential proteins involved in this process are being identified. Coronavirus transcription requires discontinuous RNA synthesis to link subgenomic RNA leader to coding sequences, a process similar to high copy-choice similarity-assisted RNA recombination. Based on a large amount of data generated by reverse genetics, our laboratory has proposed a transcription mechanism. We have proven that baseparing between the nascent RNA chain and the leader regulates the amount or subgenomic RNA produced. Nevertheless, there are additional regulatory mechanisms that influence the amount of subgenomic RNA, such as RNA-protein interactions. A major target of our program is to study the role of RNA chaperones in template switch during viral RNA synthesis.

In our second major area of work, virus-host interaction, we have postulated that specific virus structural proteins, such as the virus nucleoprotein that has been found in the cell

nucleus, and non-essential viral proteins, modulate these interactions. Using reverse genetic approaches, based on two infectious cDNA clones produced in our laboratory for TGEV and SARS-CoV, we are studying the influence of coronavirus genes on virus attenuation, cell cycle, and on relevant host functions such as immune response. Comparative genomic and proteomic information is essential in these studies.

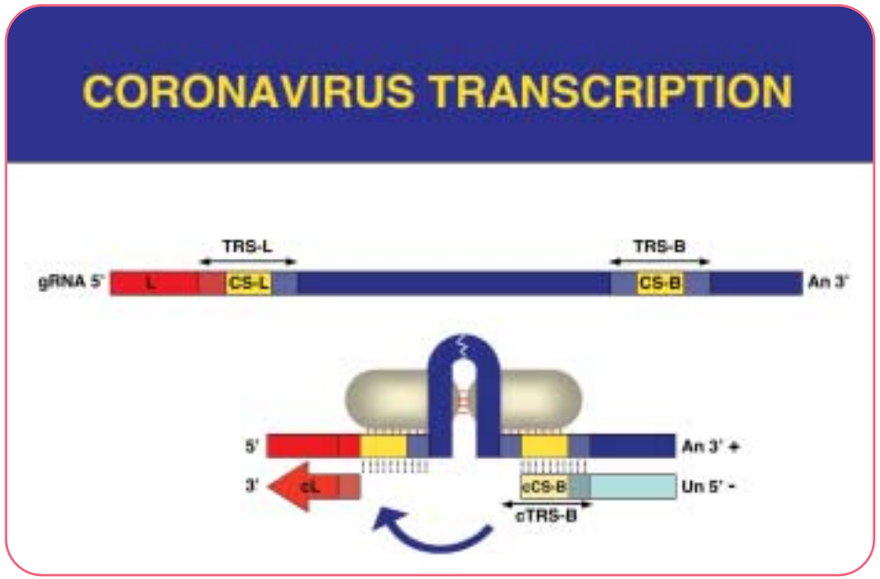

Figure 1. Diagram of the elements involved in coronavirus transcription. In the top bar, the sequence elements involved in the discontinuous synthesis of the negative RNA strand. CS-L and CS-B, leader and body CSs. TRS-L and TRS-B, transcription regulating sequences from leader and body. An, Poly A. In the lower part of the figure, an scheme of the discontinuous transcription during negative strand synthesis and of the sequence elements involved is represented. CS-B and cTRS-B represents the CS-B and cTRS-B complementary sequences, respectively. Un, Poly U. C. Leader and body sequences are probably located in close proximity in higher order structures maintained by RNA-protein and protein-to-protein interactions.

PERSONNEL

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Nº Registro: CECT 5265(P 9902673).