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RNA packaging in lentiviruses

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The selection by a lentivirus of its genomic RNA from the background of a vast excess of cellular messenger RNAs and sub-genomic viral RNAs occurs with high specificity. The nature and site of the specific interaction between the unspliced RNA genome and the gag polyprotein, which is responsible for its capture, is still poorly understood and the routes by which the two partners arrive at the initial site of interaction and what happens thereafter are similarly obscure. We have been studying this process in a number of different lentiviruses including HIV-1, HIV-2, SIV and FIV. A number of common themes emerge. Specificity of the interaction depends on RNA motifs, commonly short runs of purines in the context of specific structures. The cis-acting packaging signal structures are at the 5' end of the genome but may be upstream or downstream of the major splice donor, hence they may require additional mechanisms for specificity in some cases. The 5' structured untranslated region, together with sequences stretching into the *gag* open reading frame appear to be able to form more than one structure commonly involving long-range interactions and the different structures may contribute to the different functions of spliced and unspliced RNA. Different structures also very likely form at different stages of the passage of the genomic RNA from transcription through to encapsidation, reflecting interactions with different cellular chaperone proteins as well as trans acting viral proteins involved in trafficking of the RNA through the cell. There is good evidence for significant structural change occurring when the RNA interacts with protein ligands such as the Gag and the degree of conformational change may be quite profound. There is a close link between RNA dimerisation and packaging and it seems likely that the RNA is initially packaged as a dimer, however, whether RNA dimerisation is a necessary step for packaging is less clear and evidence from some viral systems, including HIV-2, suggests that the link with packaging is more critical to ensure a dimeric genome is present for maximum infectivity of the virus when it enters the next host cell. Newer structural analytical techniques are teaching us more about the nature of the RNA genome and its structural changes during the packaging process.