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HDV RNA Replication: Ancient Relic or Primer?

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Abstract HDV replicates its circular RNA genome using a double rolling-circle mechanism and transcribes a hepatitis delta antigen-encodeing mRNA from the same RNA template during its life cycle. Both processes are carried out by RNA-dependent RNA synthesis despite the fact that HDV does not encode an RNA-dependent RNA polymerase (RdRP). Cellular RNA polymerase II has long been implicated in these processes. Recent findings, however, have shown that the syntheses of genomic and antigenomic RNA strands have different metabolic requirements, including sensitives to α-amanitin and the site of synthesis. Evidence is summarized here for the involvement of other cellular polymerases, probably pol I, in the synthesis of antigenomic RNA strand. The ability of mammalian cells to replicate HDV RNA implies that RNA-dependent RNA synthesis was preserved throughout evolution.

1 Introduction

Early life is thought likely to have been RNA-based, a phase commonly referred to as 'the RNA world'. Clearly, a means must have existed that permitted these

primordial RNA molecules to be copied. Today, however, RNA-dependent RNA copying is regarded as a process reserved exclusively for RNA viruses, but not cellular RNAs. Virtually all RNA viruses (except retroviruses) undergo RNA-dependent RNA replication by a virus-encoded RNA-dependent RNA polymerase (RdRp), which specifically replicates the viral RNA genome but nothing else. Even satellite viral RNAs, which do not encode their own polymerase, rely on RdRp provided by the coexisting helper virus for their replication. The exceptions to this are hepatitis delta virus (HDV) and the small infectious agents of plants, viroids, neither of which encode an RdRp. Nevertheless, they undergo robust RNA replication once inside the cells.

Increasing evidence is emerging to suggest that the ability of cells to copy RNA was not lost in antiquity after all. Most of this comes from plants and lower animal species that have been shown to encode RdRps. These RdRps could potentially be responsible for viroid replication and are also thought to be involved in gene silencing by amplifying the short pieces of RNA prepared by the dicer complex. However, very recently, results in arabidopsis suggest that these cellular RdRps may, in addition, be responsible for maintaining a novel extra-genomic cache of sequence information from generation to generation (Lolle et al. 2005).

In contrast, mammalian cells have not been shown to encode any RdRps. Thus, the mechanism of HDV RNA replication is still a mystery although cellular enzymes must be responsible. In this article, evidence from our and other laboratories will be reviewed that indicate that HDV RNA replication likely occurs via a redirection of host cell DNA-dependent RNA polymerases. HDV RNA replication represents the first example of RNA copying in mammalian cells; thus, the study of this system may provide a primer to the understanding of what may turn out to be a much more widespread phenomenon.

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Hepatitis Delta Virus Background

HDV was discovered following the detection of a novel antigen-antibody system in hepatitis B virus (HBV) carriers (Rizetto et al. 1977). Currently, HDV is classified as a subviral satellite of HBV due to an obligate relationship with HBV infections in nature. However, unlike other satellite viruses, the dependence of HDV on HBV is limited solely to the provision of an envelope of hepatitis B surface antigen for virus assembly. Nevertheless, this dependence requires that natural HDV infections occur as either a co-infection with HBV or as a super-infection of HBV carriers, with the resultant disease usually being more severe than that with HBV alone. Following HDV infection, the