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Review

African swine fever virus transcription

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ABSTRACT

African swine fever virus (ASFV), a large, enveloped, icosahedral dsDNA virus, is currently the only known DNA-containing arbovirus and the only recognized member of the family *Asfarviridae*. Its genome encodes more than 150 open reading frames that are densely distributed, separated by short intergenic regions. ASFV gene expression follows a complex temporal programming. Four classes of mRNAs have been identified by its distinctive accumulation kinetics. Gene transcription is coordinated with DNA replication that acts as the main switch on ASFV gene expression. Immediate early and early genes are expressed before the onset of DNA replication, whereas intermediate and late genes are expressed afterwards. ASFV mRNAs have a cap 1 structure at its 5′-end and a short poly(A) tail on its 3′-end. Transcription initiation and termination occurs at very precise positions within the genome, producing transcripts of definite length throughout the expression program. ASFV devotes approximately 20% of its genome to encode the 20 genes currently considered to be involved in the transcription and modification of its mRNAs. This transcriptional machinery gives to ASFV a remarkable independence from its host and an accurate positional and temporal control of its gene expression. Here, we review the components of the ASFV transcriptional apparatus, its expression strategies and the relevant data about the transcriptional cis-acting control sequences.

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1. Introduction

African swine fever virus (ASFV) is a large (≈200 nm), enveloped, icosahedral double-stranded DNA virus with a lineal genome that varies in size from 170 to 190 kbp depending on the strain, and contains terminal inverted repeats and covalently closed ends (Sogo et al., 1984; González et al., 1986; reviewed in Tulman et al., 2009).

The natural hosts of this virus are the wild swine warthogs, bushpigs and the argasid ticks of the genus *Ornithodoros*. The infection of ASFV in these hosts results in a mild disease, often asymptomatic, with low viremia titers, that in many cases develops into a persistent infection (Anderson et al., 1998; Boinas et al., 2011; Kleiboeker et al., 1998; Thomson et al., 1980; reviewed by Penrith and Vosloo, 2009). In contrast, infection of domestic pigs leads to a lethal hemorrhagic fever for which the only available methods of disease control are the quarantine of the affected area and the elimination of the infected animals (Penrith and Vosloo, 2009).

The strains completely sequenced encode between 151 and 167 open reading frames closely spaced along both chains of the viral DNA. About half of them lack any known or predictable function (Chapman et al., 2008; Yáñez et al., 1995). It is currently the only known DNA-containing arbovirus and the only recognized member of the family *Asfarviridae* (Dixon et al., 2012). It has been recently reported the complete sequence of the type B DNA polymerase (PolB) gene of *Heterocapsa circularisquama* DNA virus (HcDNAV, Ogata et al., 2009) that shows a remarkable similarity with the PolB sequence of ASFV. HcDNAV is a marine virus that lytically infects the dinoflagellate *H. circularisquama* (Nagasaki et al., 2003; Tarutani et al., 2001), an abundant and ubiquitous unicellular eukaryotic component of the marine environments (Falkowski et al., 2004). HcDNAV is also a large (180–210 nm) icosahedral dsDNA virus, but possesses a larger genome than ASFV (≈356-kpb). Sequence searches and phylogenetic analyses with a partial sequence of the putative RNA Polymerase gene of HcDNAV also produce a monophyletic grouping between ASFV and HcDNAV, suggesting that HcDNAV is a new member of the *Asfarviridae* family (Ogata et al., 2009). These results, together with the data from a recent survey of the oceanic virome that found several PolB-like sequences closely related to the PolB sequence of ASFV, suggest that ASFV had its evolutionary origin in the marine environments (Monier et al., 2008).

Comparative genome analysis indicates that ASFV belongs to nucleocytoplasmic large DNA viruses (NCLDVs), a apparently monophyletic viral group infecting a broad variety of eukaryotes, that currently includes the six virus families *Asfarviridae, Ascoviridae, Iridoviridae, Phycodnaviridae, Poxviridae, Mimiviridae* and the proposed family *Marseilleviridae* (Iyer et al., 2001, 2006; Koonin and Yutin, 2010). The members of these families either have and exclusively cytoplasmic replication, or it is initiated in the nucleus and is later completed in the cytoplasm of the infected cell; some of them are relatively independent of the host cell transcriptional machinery for replication. Lineage-specific gene loss and gain within the NCLDV families, including horizontal gene transfer across the three cellular domains (Filée et al., 2008; Moreira and Brochier-Armanet, 2008)), and possibly horizontal gene exchange of essential genes among viruses from different families (Yutin et al., 2009), is thought to have contributed to the highly diverse characteristics of present-day forms, which complicates the establishment of their true evolutionary relationship. Although this is particularly true for ASFV, being the only available representative of the *Asfarviridae* family, ASFV is consistently paired along with poxvirus as sister groups (Iyer et al., 2001, 2006; Koonin and Yutin, 2010).

Despite the fact that they are morphologically very different, poxvirus and ASFV share numerous biological characteristics like its genome structure and their almost complete independence on their hosts for genome replication and gene transcription.

Poxvirus replication is strictly cytoplasmic, although some nuclear proteins are an essential part of the poxviral transcription machinery (Broyles et al., 1999; Rosales et al., 1994b; Wright et al., 2001). Despite the fact that a brief nuclear phase has been proposed for ASFV (Ballester et al., 2011; Garcia-Beato et al., 1992a; Rojo et al., 1999), most of the replication and all the viral morphogenesis takes place in the cytoplasm of the infected cell. Neither virus possesses introns.

ASFV devotes approximately 20% of its genome to encode the 20 genes currently considered to be involved in the transcription and modification of its mRNAs. This transcriptional machinery gives ASFV a remarkable independence from its host and an accurate positional and temporal control of its gene expression. Here, we review the components of the ASFV transcriptional apparatus, its expression strategies and the relevant data about the transcriptional cis-acting control sequences.

2. ASFV proteins implicated in RNA transcription and modification

Very little experimental characterization has been conducted on the genes of the proteins involved in ASFV transcription. With the exception of the identification of the guanylyltransferase activity on protein pNP868R (Pena et al., 1993) and the mRNA decapping activity on protein pD250R (Parrish et al., 2009) most of the information gathered on Table 1 comes from the comparative analysis of sequence databases (Chapman et al., 2008; Dixon et al., 1994; Yáñez et al., 1995). Particularly helpful in this regard has been the effort realized in the establishment and characterization of the NCLDV group (Iyer et al., 2001, 2006; Yutin et al., 2009). For most