Cap-Independent Translation in Adenovirus Infected Cells

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1 Adenovirus Life Cycle

Adenoviruses (Ads) are DNA viruses that infect humans, animals and birds, with different serotypes displaying different tissue tropisms (BELADI 1972). Ad was originally isolated because infection results in cytopathic effects and alterations in basic cellular metabolism. The Ad genome is temporally organized into early and late transcription units that are activated before or with the onset of viral DNA replication, respectively. Six early transcription units encode products required for productive viral replication and transformation of the infected cell. Regions E1A and E1B are required for cellular transformation and transactivation of the other viral transcription units (FLINT and SHENK 1989). Regions E2A and E2B are required for adenoviral DNA replication. Regions E3 and E4 are required for a variety of early viral functions, including suppression of histocompatibility antigen expression (reviewed in WOLD and GOODING 1991), transcriptional transactivation and regulation of nuclear to cytoplasmic transport of cellular and viral mRNAs.

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The products of the early transcription units comprise only a very minor proportion of cellular mRNA and protein synthesis, and there is no evidence for selective viral translation or inhibition of cell protein synthesis during the early part of the Ad life cycle.

The late phase of Ad infection is marked by viral DNA replication, initiating at 10–16 h after infection. Whereas early viral transcription is initiated from promoters dispersed throughout the viral genome, there is a single major late promoter (MLP), located at 16.4 map units on the viral genome, that is activated by DNA replication. The MLP generates five families of late transcripts (L1–L5) by differential splicing and polyadenylation of a large primary transcript that terminates within the right end of the genome at 99 map units (reviewed in Ginsberg 1984). Every late viral mRNA contains a common 5' noncoding region of 200 nucleotides called the tripartite leader (Berget et al. 1977), derived by splicing three small exons located upstream of the late transcripts. Most of the late Ad mRNAs encode structural polypeptides involved in packaging viral genomic DNAs that comprise the viral particle. Ad also synthesizes large amounts of two viral encoded RNA polymerase III products during late infection called virion-associated (VA) RNAs I and II (reviewed in Thimmappaya et al. 1993; Mathews and Shenk 1991). VA RNA I is required for translation of mRNAs at late times during infection because it counters a cellular antiviral response mediated by the interferon stimulated p68 kinase.

Ad infection of cells in culture occupies a life cycle lasting about 2–4 days, during which time large quantities of late viral polypeptides and infectious particles are produced. The late phase of infection is associated with almost exclusive translation of late Ad mRNAs and inhibition of cell protein synthesis (reviewed in Schneider and Zhang 1993), and impaired transport of cellular mRNAs from the nucleus to cytoplasm (Beltz and Flint 1979). Cellular synthesis of DNA, RNA and proteins is usurped for the production and assembly of viral particles which are released when cell lysis occurs. The block to cellular protein synthesis occurs during progression into the late phase of Ad replication. Late viral mRNAs generally represent the majority (∼90%–95%) found in polyribosomes, but only a fraction of the total cytoplasmic pool of mRNAs (reviewed in Schneider and Zhang 1993). Therefore cellular mRNAs are suppressed from translating and late Ad tripartite leader mRNAs are preferentially used.

Ad inhibition of cellular translation is not related to the viral block in transport of host mRNAs from the nucleus to cytoplasm. Studies showed that the cytoplasmic abundance of most cell mRNAs does not significantly decline during late infection (Babich et al. 1983). It was also shown that Ad inhibition of cellular protein synthesis can be prevented by the drug 2-aminopurine without relieving the normal block in transport of host mRNAs (Huang and Schneider 1990). These results imply that translation of cellular mRNAs is specifically prevented during late Ad infection while late Ad mRNAs are preferentially utilized.