1 Introduction

For more than 15 years human adenoviruses (Ad) have been a powerful tool for studying cellular processes such as regulation of gene expression, alternative splicing, polyadenylation, and replication. Especially the analysis of viral proteins encoded by early region 1A (E1A), which was shown to regulate transcription, has given many insights into how DNA viruses regulate their own and cellular gene expression. Moreover, E1A proteins have been the subject of extensive studies because of their ability to act as oncoproteins that cooperate with the adenovirus E1B gene products to transform rodent cells in culture and, in case of the
oncogenic adenoviruses (e.g., Ad12), to induce tumors in animals (GALLIMORE et al. 1974; GRAHAM et al. 1974a, b; HOUWELING 1980; JOCHEMSEN et al. 1982). The ability to promote oncogenic transformation and transcriptional regulation appear to be distinct activities of the E1A polypeptides (for review see MORAN and MATHEWS 1987). In oncogenic transformation, protein functions of region E1A are necessary to immortalize primary cells, whereas functions of region E1B are essential to obtain a fully transformed phenotype. The functions of region E1B can be substituted by specific cellular gene products, e.g., activated Ha-ras (BYRD et al. 1988; RULEY 1983). The reasons for the difference in oncogenicity of variant adenovirus serotypes are not yet understood.

The E1A proteins are by far the most extensively studied viral transcriptional regulators. All adenoviral promoters that have been examined respond to E1A proteins, but also specific cellular promoters are transcriptionally regulated. The most striking property to emerge from subsequent studies has been the wide range of promoters on which the E1A proteins can act. Although they do not exhibit sequence-specific DNA-binding activity, they do bind to DNA apparently independent of sequence (FERGUSON et al. 1985). The regulated promoters share no common sequence elements, implying that the trans-regulation is not mediated through interaction of E1A proteins with a specific E1A response promoter element.

In this review we will focus on the functions and on gene regulatory mechanisms of E1A gene products encoded by the oncogenic adenovirus serotype 12 and compare these functions with those of non-oncogenic serotypes.

2 Structural and General Properties of the Adenovirus Type 12 E1A Proteins

E1A, located at the leftmost end (0%–11.5%) of the adenovirus genome, is the first transcription unit to be expressed after infection of recipient cells (LEWIS and MATHEWS 1980; NEVINS et al. 1979). By alternative splicing of a common Ad12 E1A RNA precursor, at least six different mRNA are generated (13S, 12S, 11S, 10S, 9.5S, and 9S, according to their sedimentation coefficients; Fig. 1; PERRICAUDET et al. 1980; SAWADA and FUJINAGA 1980; BROCKMANN et al. 1990). All mRNA share the same 5' and 3' ends, but differ in the amount of internal sequences removed by splicing events. At least five distinct proteins of 266 amino acid residues (R) (13S mRNA), 235R (12S mRNA), 106R (11S and 10S mRNA), 52R (9.5S mRNA), and 53R (9S mRNA) are translated from the respective mRNA. The protein products translated from the 13S and 12S mRNA share the same N- and C-terminal sequences and differ only in a 31R internal, cysteine-rich segment, unique to the larger E1A protein. This segment represents one out of three E1A domains which are highly conserved among distantly related human adenoviruses (KIMELMANN et al. 1985), termed conserved regions 1, 2, and 3 (CR1, CR2, CR3).