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Papillomavirus transcripts and posttranscriptional regulation

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ABSTRACT

Papillomavirus gene expression is strictly linked to the differentiation state of the infected cell and is highly regulated at the level of transcription and RNA processing. All papillomaviruses make extensive use of alternative mRNA polyadenylation and splicing to control gene expression. This chapter contains a compilation of all known alternatively spliced papillomavirus mRNAs and it summarizes our current knowledge of viral RNA elements, and viral and cellular factors that control papillomavirus mRNA processing.

Introduction

Papillomaviruses are small DNA viruses with a circular double stranded DNA genome (zur Hausen, 2002). Their genomes typically encode early and late genes that are expressed in a temporal and highly regulated manner (Howley and Lowy, 2006). Gene expression is regulated at the level of transcription (Bernard, 2002; Thierry, 2009) and RNA processing (Graham, 2008; Schwartz, 2008; Zheng and Baker, 2006) and the papillomavirus proteins are produced from a myriad of alternatively spliced and polyadenylated mRNAs. Maps of all known papillomavirus mRNAs are shown in Appendix I. Advantages of the extensive use of alternative splicing and polyadenylation include the ability to express many genes from a compact genome, as well as the ability to individually regulate expression of each gene during the viral life cycle. Papillomavirus gene expression is tightly linked to the differentiation program of infected epithelial cells. The most obvious example is perhaps the well-conserved delay in late L1 and L2 gene expression to the uppermost layers with terminally differentiated cells in the squamous epithelium (Chow et al., 2010; Doorbar, 2005; Moody and Laimins, 2010). Activation of L1 and L2 expression requires a viral promoter-switch, a change of polyA signal and derepression of two alternative splice sites. Merely a promoter switch does not suffice, as experiments in which the late HPV-16 promoter p670 was replaced by the constitutively active human cytomegalovirus promoter did not activate late gene expression (Orru et al., 2012; Zhao et al., 2004). Therefore, regulation at the level of RNA processing plays an important role in papillomavirus gene expression. Furthermore, HIV-1 Rev and RRE that are required for efficient nuclear export of partially spliced HIV-1 mRNAs (Felber and Pavlakis, 1993), enhance BPV-1, HPV-1 and HPV-16 late gene expression (Barksdale and Baker, 1995; Tan et al., 1995; Tan and Schwartz, 1995), and adenovirus E4orf4 that regulates the switch from early to late gene expression in adenoviruses by dephosphorylating splicing factors (Akusjarvi and Stevenin, 2003), can induce HPV-16 L1 mRNA production by enhancing viral mRNA splicing (Somberg et al., 2009). Significant effects on papillomavirus gene expression by relatively subtle mutations at RNA processing signals in complete papillomavirus genomes of different types have been reported (Andrew and DiMaio, 1993; Deng et al., 2003; Hubert and Laimins, 2002; Klumpp et al., 1997; Poppelreuther et al., 2007; Terhune et al., 2001, 1999). These results underscore the importance of RNA processing in the papillomavirus gene expression program. This chapter discusses cis-acting papillomavirus RNA elements and viral and cellular trans-acting factors that regulate papillomavirus gene expression.

RNA elements in papillomavirus late and early 3′-UTR sequences

Late 3′-UTR sequences

Inhibitory sequences in the late untranslated region of papillomavirus mRNA were originally discovered in BPV-1 and in HPV-16 (Furth and Baker, 1991; Kennedy et al., 1990, 1991) and are relatively well characterized (Graham, 2008). One may speculate that the role of these sequences in the viral life cycle is either to prevent premature late gene expression or to serve as landing pads for cellular RNA binding proteins that activate late gene expression in response to cellular differentiation. Inhibitory sequences are present in the late 3′-UTR of all HPVs that have been analyzed, including HPV-1, HPV-2, HPV-6, HPV-16, HPV-18, HPV-31, HPV-41 and HPV-61 (Cumming et al., 2002; Kennedy et al., 1990, 1991; Tan and Schwartz,

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1995; Zhao et al., 2007b). In general, these sequences are not well conserved but many are AU- or GU-rich and often contain multiple copies of the G-U_{3-5}-G sequence which resembles the AUUUA-motif often found in AU-rich RNA instability elements in the 3′-UTR on cellular mRNAs (Zhao et al., 2007b). These late UTR elements have an inhibitory function in mitotic cells including cancer cells that must be overcome in terminally differentiated cells that are permissive for late gene expression. Best characterized are the late UTR elements in BPV-1 (Fig. 1), HPV-1 (Fig. 2) and HPV-16 (Figs. 3 and 4).

It is well established that the negative element in the BPV-1 late UTR is a relatively short, 5′-splice site-like sequence that binds specifically to the U1snRNA part of the cellular U1snRNP complex (Fig. 1) (Furth et al., 1994). This binding inhibits polyadenylation of the late BPV-1 mRNAs (Furth et al., 1994; Gunderson et al., 1998). In contrast, the inhibitory element in the HPV-1 late UTR is a classical AU-rich RNA instability element (ARE) (Fig. 2) (Sokolowski et al., 1997; Tan and Schwartz, 1995), similar to those originally discovered in a subset of short-lived cellular mRNAs,

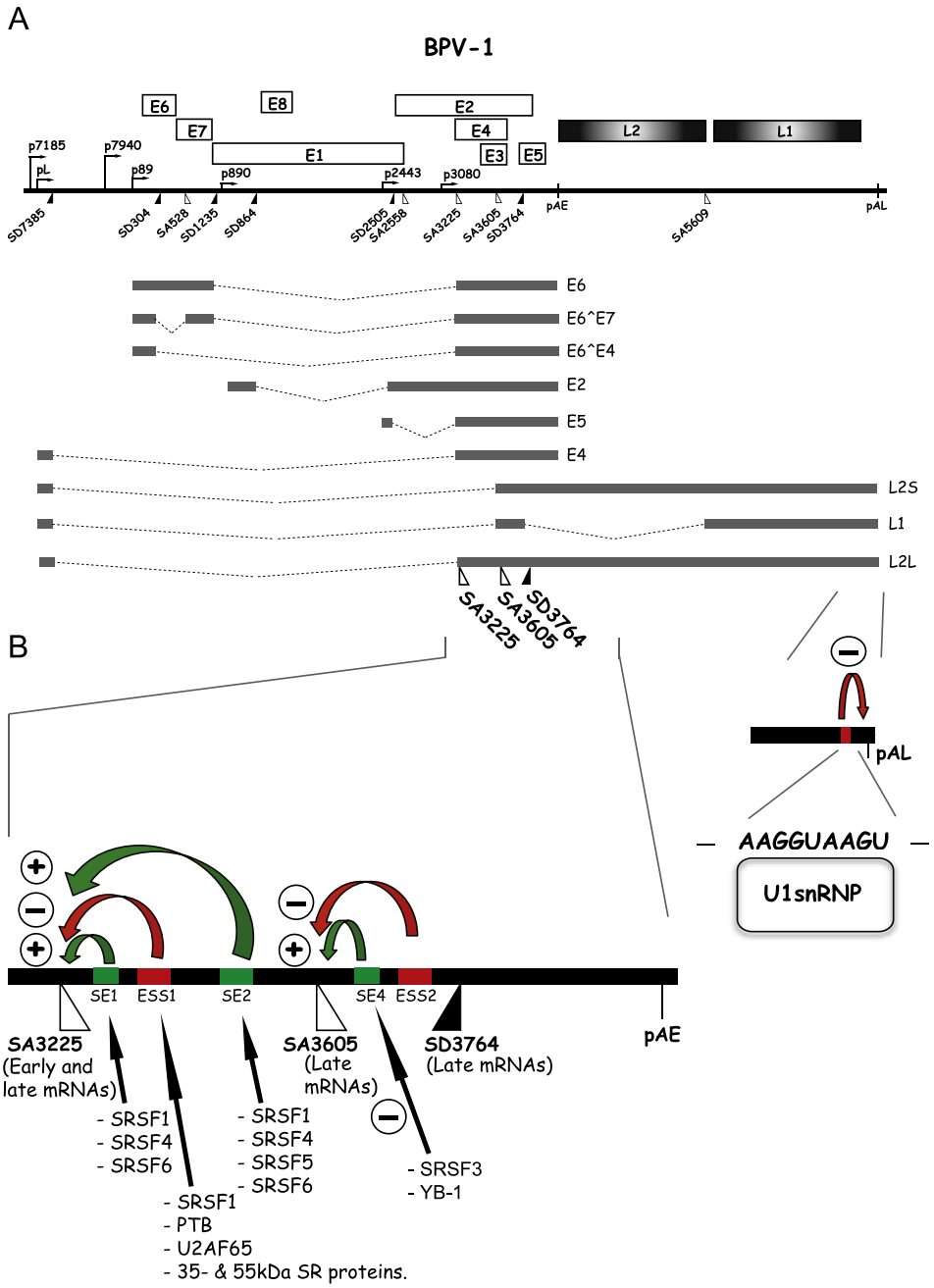

Fig. 1. (A) Schematic drawing of the BPV-1 genome. Boxes represent protein coding sequences, arrows promoters and black and white triangles, 5′- and 3′-splice sites, respectively. Early and late polyA signals named pAE and pAL are indicated. A subset of viral mRNAs is shown below the genome and the most likely translation product for each mRNA is indicated to the right. (B) Left: The positions of splicing silencer (red) (ESS1 and ESS2) and splicing enhancer (green) (SE1, SE2 and SE4) elements and the cellular proteins they interact with are indicated (Zheng and Baker, 2006). See text for details and Table 1 for SR-protein nomenclature (Manley and Krainer, 2010). Colored arrows show the effect of the regulatory RNA elements on the various BPV-1 splice sites. Right: The BPV-1 late UTR encodes a negative regulatory RNA element that binds specifically to cellular U1snRNP. This interaction inhibits late mRNA processing. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)