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Minireview

Transcriptional regulation of the papillomavirus oncogenes by cellular and viral transcription factors in cervical carcinoma

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ABSTRACT

Human papillomaviruses (HPV) are small DNA viruses that contain a compact and non-redundant genome. HPV, with the help of only few genes, can achieve a complete vegetative cycle specifically in the epidermal and mucosal keratinocytes. Modification of the host cell transcriptional regulation is one of the major ways to regulate the viral production and maturation. The vegetative cycle of papillomaviruses is linked to terminal differentiation of the epithelium and is dependent on the host cell regulatory networks for transcriptional control. The mucosal high risk HPV16 and HPV18 types have been the main models to explore this transcriptional regulation mainly because they are prevalent in cervical cancer as the best studied virally induced cancers in human. In addition, the availability of cell lines, grown from cervical cancers containing integrated HPV16 or 18, represent versatile in vitro models for transcription studies. We will describe here some aspects of the transcriptional regulation that contribute to cell specificity, the basis of which is not yet fully understood despite efforts of numerous groups during the past two decades. Another specificity of small DNA viruses is the multifunctional characteristics of their regulatory proteins due to extreme genomic constraint. We will describe the role played by the viral E2 proteins in the transcriptional repression of the high risk HPV oncogenes and its implication in cervical cancer.

Transcriptional regulation of the HPV early genes in cervical cancer

A basic feature of HPV associated cancer cells is that part of the viral genome is integrated in the host cell genome. Conserved characteristics of this integration include tandem repeats from a single to several hundreds copies, of the viral DNA at random locations in the cellular genome. Usually only a segment of the viral genome is integrated containing the regulatory region or "Long Control Region" also called "LCR", and part of the early region, including the E6 and E7 open reading frames encoding the two main oncogenes. These two genes are transcribed in at least two messengers initiated at a unique promoter contained within the viral regulatory region called P_{105} for HPV18 and P_{97} for HPV16 and HPV31, located immediately upstream of the E6 open reading frame. Another important aspect of this integration is the disruption of the open reading frames of E1 and/or E2 downstream to the E7 gene. Since E1 and E2 are the two proteins involved in viral DNA replication, integration leads to disruption of viral DNA replication. At the same time, and since E2 has been shown to repress E6 and E7 transcription through repression of the viral early promoter (Thierry and Yaniv, 1987), disruption of E2 results in transcriptional activation of the E6 and E7 oncogenes in cervical cancer. Consequently, transcription of E6 and E7 in cervical carcinoma cells is positively controlled by cellular transcription factors rather than by viral transcription factors.

Structure and function of the HPV early promoter

The early promoter was named after the genomic sequence with numbering corresponding to the 5′ end of the E6 and E7 messenger RNA which are nucleotide 105 for HPV18 and 97 for HPV16 and HPV31 for instance. These early messengers exhibit very short if any leader sequences. For instance, in HPV18, nucleotide 105 coincides with the A of the ATG initiation codon of the E6 open reading frame (Thierry et al. 1987). As expected for RNA Polymerase II promoters, a consensus TATA box is present in the viral promoter, upstream of the transcription initiation site, that recruits the TFIID general transcription factor. Upstream sequences of this TATA box contain a transcriptional enhancer to which cellular transcription factors bind (Garcia-Carranca et al., 1988; Gloss et al., 1987; Swift et al., 1987). Sequences of these enhancers and the transcription factors involved are only partly conserved among mucosal HPVs, although these viruses exhibit the same host restriction. Among elements distinctively conserved in the mucosal HPV genomes are the sequences and locations of the binding sites for the viral E2 proteins. There are four of them distributed in the regulatory regions at comparable locations upstream of the initiation site, with two tandem repeated sites located 3 or 4 nucleotides upstream of the TATA box. This unique distribution of the E2 binding

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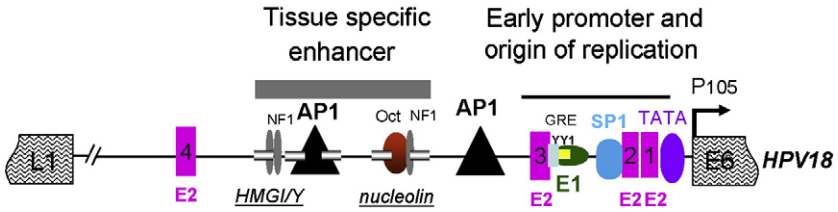

Fig. 1. Schematic representation of the HPV18 regulatory region with the binding sites for transcription factors represented. The four E2 binding sites are shown and their disposition and spacing are conserved among mucosal HPV types as well as the TATA box binding the general transcription factor TFIID and the SP1 binding sites. The E1 binding site defined the origin of replication together with the adjacent E2 binding sites. The core enhancer sequence is shown containing AP1 which has been shown to be involved in regulation of several other HPV types and HMGI/Y and nucleolin which are more specific for the HPV18 transcription, GRE (Gloss et al., 1987; Medina-Martinez et al., 1996), YY1 and C/EBP beta (Bauknecht et al., 1992; Bauknecht et al., 1996) and NF1 (Chong et al., 1991) are also shown.

sites in the viral regulatory regions is a landmark of mucosal HPV whereas in other papillomaviruses their numbers and locations vary (Sanchez et al. 2008) (Fig. 1). The exact role played by E2 in transcriptional regulation in these various models is however not yet fully understood. E2 has been demonstrated to be a transcriptional activator of early genes in the bovine BPV1 and a repressor of early genes in the human mucosal HPV (Spalholz et al., 1985; Thierry and Yaniv, 1987).

The emerging picture of HPV early promoter transcription can therefore be recapitulated by two points: first, activation by an array of cellular transcription factors binding to a regulatory region upstream of an RNA Polymerase II promoter and second, repression by binding of the viral E2 transcription factor to sites within the promoter itself. Mechanisms involved in both of these regulatory pathways have been extensively studied although several aspects remain unclear. For instance, and this can be considered as one of the major flaw in our knowledge regarding HPV transcription, the keratinocyte specificity is not yet fully understood. Indeed many transcription factors involved in HPV transcription have been described over the years since the first depiction of the HPV 18 early promoter, more than 20 years ago in 1987, (Thierry et al., 1987) but none of them are cell specific, although their combination may exhibit a certain level of specificity.

The cellular transcription factors

Among the main players involved in HPV transcription are the ubiquitous transcription factors SP1 (Gloss and Bernard, 1990; Hoppe-Seyler and Butz, 1992) and AP1 (Thierry et al., 1992). Both have been found to play a critical role in mucosal HPV including high risk types 18, 16, 31, or low risks types 6 and 11 as their binding sites can be found in the regulatory regions of the mucosal HPVs. SP1 is a ubiquitous transcription factor which is involved in the transcriptional regulation of as many as 30% of the cellular genes (Cawley et al., 2004). Its GC rich binding site is generally found in the promoter regions, close to the transcriptional initiation site but not in the enhancers, as reviewed in Wierstra (2008). In the mucosal HPV genomes, SP1 is found just upstream of the E2 binding sites, part of its binding sequence overlapping with E2 binding. This specific arrangement, together with the close proximity of the E2 binding sites to the TATA box, (Fig. 1) is probably involved in transcriptional repression as the binding of E2 resulted in steric hindrance which prevented the formation of the transcriptional initiation complex by displacing TFIID and Sp1.

In contrast, AP1 is frequently involved in enhancer function and is constituted by heterodimers of Jun and Fos proteins belonging to two different families of proto-oncogenes. AP1 are also quasi-ubiquitous transcription factors whose activities are modulated through signal transduction, thus providing a large range of regulatory potentialities. Further levels of modulation of AP1 activities are mediated through differential expression of the factors belonging to the two families in different tissues and specific interaction with other transcription factors, reviewed in Zenz and Wagner (2006) and Hess et al. (2004). Interaction of AP1 with other transcription factors can occur upon cooperative binding to adjacent sites inducing specific and synergistic transcriptional activation, for instance with the HMGI/Y factor, as described for the HPV18 enhancer (Bouallaga et al., 2000). HMGI/Y is an architectural transcription factor highly expressed in cancer and more particularly in cervical carcinoma, thus inducing a strong activation of the E6 and E7 transcription in these cells (Bouallaga et al., 2000). Interestingly, E7 induces transcriptional activation of HMGI/Y through E2F activation, as found in microarray analyses (Thierry et al., 2004), thus indicating that an auto-activating loop may allow amplification of the E7 transcription in cervical carcinoma. The AP1 and HMGI/Y binding sites are central to a three dimensional structure called enhanceosome which is formed in the HPV18 regulatory region (Bouallaga et al., 2000) and was first described in 1995 for two cellular genes, IFN beta (Falvo et al., 1995; Thanos and Maniatis, 1995) and TCR alpha (Giese et al., 1995). It is not possible at the moment to extend this concept to the other mucosal HPVs, although AP1 binding sites have been found in all HPV regulatory regions studied so far. Recruitment of the CBP/p300 histone acetylase coactivator by the HPV18 enhanceosome has also been shown in cervical carcinoma cells (Bouallaga et al., 2003) but nothing is known, at the moment, regarding the putative role of these coactivators in keratinocytes. The central function of the AP1 transcription factors in keratinocyte differentiation and their involvement in the regulation of several specific cellular genes such as involucrin, loricrin, cytokeratins or integrins, highlighted their putative crucial function in this cell type specific papillomavirus transcriptional control. In this respect, the heterodimers modulating HPV18 expression mainly contain JunB and Fra2 which are highly expressed in keratinocytes and are modulators of their differentiation (Bouallaga et al., 2003; Mehic et al., 2005).

HPV transcription exhibits stringent cell specificity in that the viral regulatory region is not active in cell types other than keratinocytes or cervical carcinoma cells (Fig. 2). As depicted above, AP1 plays a central role in this specificity but it is not sufficient to account for the full control exerted on the HPV transcription. Other transcription factors that have been found involved such as GRE, NF1, YY1, Oct-1, C/EBP, reviewed in Hoppe-Seyler and Butz (1994) and O'Connoret al. (1995) or nucleolin for the HPV18 transcription (Grinstein et al., 2002), are not specific either and, although the hypothesis that cooperation of multiple nonspecific factors could confer specificity has been suggested, no conclusive experiments have been done so far to sustain this hypothesis. Nucleolin is an interesting example of interaction of a ubiquitous protein that might bring about specificity for dividing cells, since it activates HPV18 transcription in a cell cycle-dependent manner, which in turn might amplify the potential of E7 to activate S-phase genes. It binds the HPV18 enhancer region to an Oct-1 binding site, around 30 nucleotides downstream of the AP1 binding site, in the core enhanceosome and could therefore participate to its structure and function in cervical carcinoma (Fig. 1).

The functional significance of the transcription factors involved in HPV transcriptional regulation needs to be re-examined in vivo by

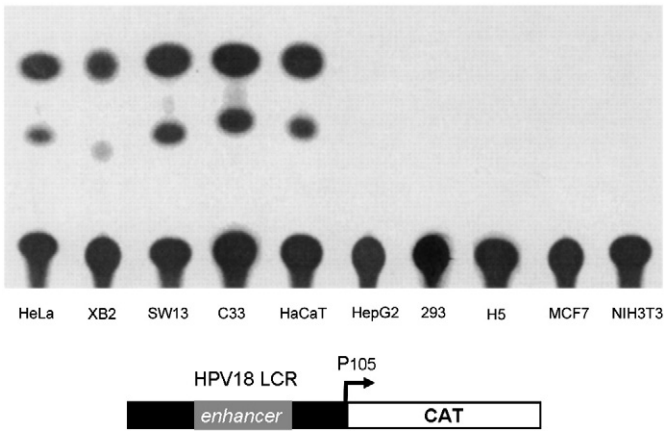

Fig. 2. Representative CAT assays of the HPV18 early promoter activity in various cell lines. In cervical carcinoma cells lines (HeLa and C33) in human (HaCaT) and mouse (XB2) keratinocytes and in an epithelial cell line (SW13), the transcription of the CAT reporter gene is high while in liver carcinoma (HepG2), embryonic transformed cells (293), human fibroblast (H5) breast adenocarcinoma (MCF7) and mouse fibroblasts (NIH3T3), no transcription can be detected. The schematic representation of the CAT reporter plasmid is shown.

use of chromatin immunoprecipitation methods in different conditions, either in cervical carcinoma cells or in keratinocytes at different stages of differentiation. Recent data indicated that C/EBP-alpha and C/EBP-beta play a role (Wooldridge and Laimins, 2008) among several other transcription factors which have also been found to bind in vivo to the regulatory region of the episomal form of HPV16 in keratinocytes (Carson and Khan, 2006). However, more work needs to be done to elucidate the basis of transcriptional cell specificity of mucosal HPV.

Transcriptional repression by the viral transcription factor E2

The full length E2 protein has originally been described as a transactivator of the BPV1 early transcription (Spalholz et al., 1985) while a shorter form, deleted of the amino terminal transactivation domain, was described as a repressor (Lambert et al., 1987). The E2 transcription factor is a specific DNA binding homodimer harbouring a classical modular structure in three distinct domains (Giri and Yaniv, 1988; Dostatni et al., 1988; McBride et al., 1989). Binding sites for E2 are present in multiple copies in various papillomavirus type regulatory regions although, as mentioned earlier, only 4 copies are found in the regulatory regions of mucosal HPVs (Sanchez et al., 2008) (Fig. 1). The distances between the four binding sites are conserved, 1 or 2 nucleotides between BS#1 and BS#2, the most proximal binding sites to the promoter, while 64 nucleotides were found between the E2 BS#2 and BS#3 and about 320 nucleotides span the BS#3 and the most distal BS#4. As for the proximity of the E2 BS to the TATA box, it is also well conserved involving 3 nucleotides for the majority of the mucosal HPV. We and others have shown that the three sites proximal to the TATA box are involved in E2 transcriptional repression of the early promoters, with a prominent role played by the two most proximal sites to the TATA box, (Romanczuk et al., 1990; Thierry and Howley, 1991; Demeret et al., 1997), while at the same time these sites are used for efficient viral DNA replication in concert with the E1 viral helicase (Demeret et al., 1995). As already mentioned, binding of E2 represses transcription through steric hindrance of the interaction with the transcriptional initiation factor TFIID at the proximal TATA box. Mechanism of transcriptional repression by E2 binding was first demonstrated in vivo in transfected cells (Romanczuk et al., 1990; Thierry and Howley, 1991) and in vitro in cell extract (Dostatni et al., 1991), as well as more recently with purified transcription factors (Hou et al., 2000), indicating that E2 binding to the HPV regulatory region precludes binding of TBP to the adjacent site.

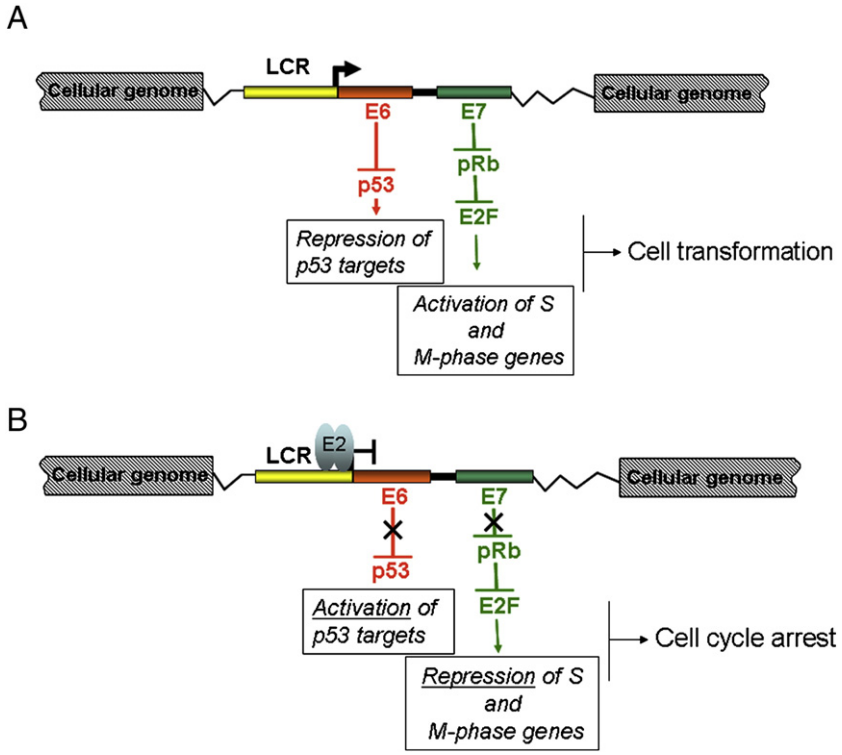

Fig. 3. Schematic representation of the fragment of HPV18 genome integrated in the cellular genome as in the HeLa cervical carcinoma cells. (A) The E6 and E7 genes are transcribed from the P105 promoter and the products of these genes negatively interfere with p53 and pRB respectively, thus inducing cell cycle deregulation and cell transformation. (B) When expressed in HeLa cells, the viral E2 transcription factor represses the E6 and E7 transcription thereby inhibiting their effects on p53 and pRB and inducing cell cycle arrest and senescence.

The structure and function of E2 as transcription factors are conserved among papillomaviruses although their roles significantly differ in regulating transcription. Specifically, HPV E2 proteins have retained fully functional transactivation domains that can activate transcription of reporter genes in heterologous expression constructs, although the transcriptional unit(s) activated in the homologous viral genomes, are unknown. Activation by E2 requires cooperation of at least two E2 dimers bound to cognate sequences which could be adjacent or distant. More recently, dimerization of the HPV16 E2 amino-terminal transactivation domain over large distances has been shown to induce looping of the intervening sequences, thus providing another potential mechanism for E2 transcriptional regulation (Hernandez-Ramon et al., 2008).

Interestingly, transcriptional repression requires an intact DNA binding domain but also involves a competent transactivation domain (Goodwin et al., 1998; Nishimura et al., 2000). This need for an intact transactivation domain to fully repress transcription is not understood yet, although it has been suggested that it might recruit transcriptional corepressors. Alternatively, the same recruited factor(s), such as the chromatin component BRD4 for instance, important for segregation of the viral genome during mitosis (You et al., 2004), could participate in transcriptional activation or repression, depending on the chromatin context (Schweiger et al., 2007) (Wu et al., 2006). Looping of the regulatory sequences through interaction of the E2 amino-terminal domains, could also be involved in the mechanism of repression (Hernandez-Ramon et al., 2008).

In this respect, distinct E2 repressor has been described in the HPV31 model, whose amino terminal domain is replaced by a fusion with the short E8 open reading frame which acts as an active repressive domain able to repress transcription as well as replication by recruiting corepressors (Ammermann et al., 2008; Stubenrauch et al., 2000). A comparable E2 repressor has also recently been described in the HPV16 model raising the possibility that such repressors could also regulate transcription during the normal viral cycle in mucosal HPV infection (Lace et al., 2008).

The roles of E2 in the viral infection and transformation

As described above, E2 is a transcription factor which binds to specific cognate sequences in the viral genome and is able to repress transcription from the HPV early promoters. This repression of the viral oncogenes is relieved after integration of part of the viral genome into the cellular genome by disruption of the E2 open reading frame (Fig. 3A). It is believed that this process therefore leads to high levels of E6 and E7 transcription as normally observed in cervical carcinoma cell lines. When E2 is re-expressed in cervical carcinoma, it represses the endogenous viral transcription leading to cell cycle arrest, apoptosis and senescence, thus establishing altogether the negative impact of E2 on carcinogenic progression and the need for the viral oncogenes to be continuously expressed to maintain cervical carcinoma cell proliferation (Fig. 3B) (Desaintes et al., 1997; Goodwin and DiMaio, 2000; Hwang et al., 1993). This E2-mediated repression of E6 and E7 transcription leads to dramatic changes in the HeLa cells transcriptome through modulations of the p53 and p63 as well as E2F transcription factors (Thierry et al., 2004; Teissier et al., 2007; Wells et al., 2003; Johung et al., 2007) (Fig. 3B).

These paradoxical requirements reflect a complex usage of the viral E2 regulator which activates replication and at the same time represses transcription by binding to the same sites. Furthermore, this binding could repress or activate transcription through interaction with similar, if not identical, cofactors. More recently, E2 has also been shown to be able to shuttle from the nucleus, where it is known to function in transcription and replication, to the cytoplasm where it activates caspase 8, thus inducing apoptosis (Blachon et al., 2005; Thierry and Demeret, 2008). In addition, E2 has also been shown to modulate the cell cycle, independently of transcription and DNA replication regulatory functions (Bellanger et al., 2005). These new functions are not conserved among mucosal HPV types and appear linked to the oncogenic potential of high risk viruses. We showed further that high risk HPVs are able to modulate the cell cycle through the E2 proteins which induce mitotic arrest by interfering with the mitotic ubiquitin ligase APC (Bellanger et al., 2005). This leads to genomic instability and could play a prominent role in the early stages of viral infection to predispose infected cells to transformation.

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I apologize to my colleagues that I could not cover all the literature on HPV transcription due to space limitation.

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