Virology ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Virology

journal homepage: www.elsevier.com/locate/yviro

Review

The 3 facets of regulation of herpes simplex virus gene expression: A critical inquiry

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ARTICLE INFO

Article history:
Received 1 December 2014
Returned to author for revisions
20 February 2015
Accepted 20 February 2015

Keywords:
Replication
Latency
Reactivation

ABSTRACT

On entry into the body herpes simplex viruses (HSV) replicate in a series of steps that involves derepression of viral DNA activated by VP16, a virion protein, and sequential transcription of viral genes in a cascade fashion. HSV also enters into neurons in which viral DNA maintained as heterochromatin and with few exceptions viral gene expression is silenced. A third face of the interaction of HSV with its host cells takes place at the moment when the silenced viral genome in neurons is abruptly derepressed. The available data do no reveal evidence that HSV encodes different regulatory programs for each facet of its interaction with its host cells. Rather the data point to significant gaps in our knowledge of the mechanisms by which each facet is initiated and the roles of the infected cells at each facet of the interaction of viral gene products with the host cell.

Contents

Introduction

If herpes simplex viruses (HSV) could unveil their moto, it would read "Multiply, Persist and Disseminate". Indeed for more than a century it has been recognized that HSV infect people by direct contact between tissues of individuals with a herpetic lesion and those of a healthy individual. In the course of multiplication at the portal of entry the virus infects nerve endings and is transported to a dorsal root or sensory neuron where it remains quasi-silent or, in the traditional terminology, latent. In some individuals the virus remains latent for a life time. In others it periodically replicates and is transported anterograde to a site at or near the portal of entry into the body where it replicates and is transmissible by contact (reviewed in Roizman et al., 2013. That HSV is successful in its endeavor to replicate, persist and disseminate is evident from the fact that in many populations the incidence of HSV-1 infections approaches 100%.This extraordinary achievement is due in large part to the exceptional control of viral gene expression during initial replication at the portal of entry, In the course of latent infection and even in the course of reactivation from latent state. In every sense of the word, HSV is a control freak. It is convenient to consider each of the 3 states of HSV sojourn in human bodies separately.

Productive infection at the portal of entry

Viral replication at the portal of entry into the body is a multicycle event that ultimately becomes arrested by the immune

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http://dx.doi.org/10.1016/j.virol.2015.02.036
0042-6822/

system. The accepted model of the events that take place in the course of a single replicative cycle is the cell culture in which most if not all cells can be synchronously infected. Current understanding of the events taking place in the infected cell may be summarized as follows:

On infection HSV brings into the cells a capsid containing DNA and approximately 20 proteins packaged in the tegument—a compartment located between the capsid and envelope (Roizman and Furlong, 1974). The capsid is transported to the nuclear pore where it releases the viral DNA into the nucleoplasm. Among tegument proteins 3, i.e. the virion host shutoff (VHS) RNase, VP16 and U_L47 are also translocated to the nucleus (Shu et al., 2013)

On entry of viral DNA into the nucleus several interrelated events take place. Foremost, DNA sensors trigger innate immune responses. A key component of the response is the induction of numerous stress response mRNAs that are degraded by VHS (Esclatine et al., 2004). A second event with significant consequences is the assembly at viral DNA of a dynamic structure designated formally as ND10 or PML bodies and regulated by the promyelocytic leukemia (PML) protein (Ishov and Maul 1996, Maul et al., 1993, 1996). A third key event is insertion of repressive modifications that preclude the expression of viral genes (Bryant et al., 2011, Cliffe et al., 2009; Knipe and Cliffe, 2008; Kristie, 2007; Huang et al., 2006; Liang et al., 2009; Silva et al., 2008; Narayanan et al., 2007).

The order of expression of viral genes. The α genes

The earliest studies focused on the order of viral gene expression in productive infection. Thus studies on the inhibitors of protein synthesis identified 5 genes expressed after infection in the absence of *de novo* protein synthesis. The products of these genes were designated as Infected Cell Proteins (ICPs) 0, 4, 22, 27, and 47 on the basis of their migration on electrophoresis in denaturing gels (Honess and Roizman, 1974, 1975). A second, much larger group of ICPs accumulated in infected cells treated with phosphonocetate, an inhibitor of viral DNA synthesis. Lastly, the early studies identified a larger group of ICPs that accumulated in infected cells in the absence of inhibitors (Honess and Roizman, 1974, 1975). In principle these groups corresponded to immediate-early, early and late nomenclature adapted from bacteriophage. The subdivisions however were more complex. Among the early protein some, (e.g. ICP8) are made very early whereas others (e.g. the thymidine kinase) are made much later. Among the late proteins some are made in small amounts in the absence of viral DNA synthesis whereas others required de novo synthesis of viral DNA in order to accumulate in infected cells. To avoid a complicated nomenclature that described these diverse groups as immediate-early, early-early, early-late, late-early and late-late they were designated as α, β_1, β_2, γ_1,and γ_2, respectively. The complexity of requirements for the sequential synthesis of viral gene products did not rest there. In recent studies it was shown that only ICP0 was made in cells depleted of the histone acetyl transferase CLOCK (Kalamvoki and Roizman 2010). In essence, these studies revealed that ICP0 recruits Bmal1 which in turn recruits its partner CLOCK to the viral transcriptome. This enables the transcription of other α genes.

Finally there is evidence that the expression of some open reading frames (e.g. ORF P and ORF O) is blocked by α proteins as are some miRNAs that accumulate preferentially in cells exposed to inhibitors of protein synthesis at the time of infection (Randall et al., 1997; Du et al., 2015).

The fundamental principle guiding the early studies on productive infections is that on entry of viral DNA into the nucleus the expression of viral genes is sequentially ordered (activated) in a cascade fashion. In quick succession α gene promoters were found to share common sequences (5 G/CTAATGAG/AATTCC/TTTGNGGG3') containing binding sites for Oct1 and VP16, a viral structural protein brought into cells along with viral DNA and a cellular protein designated Host Cell Factor 1 (HCF1). (Mackem and Roizman, 1982, Pellett et al., 1985, Kristie and Roizman, 1987, McKnight et al., 1987, Kristie and Roizman, 1988) Elegant, compelling studies have shown that VP16 enables the assembly of Oct1, HCF1 and lysine specific demethylase 1 (LSD1) along with transcriptional factors to derepress and initiate the transcription of α genes (Liang et al., 2009). LSD1 plays a key role in the derepression of α genes. In uninfected cells the protein is unstable in the absence of its partner (CoREST) (Shi et al., 2005, Yang et al., 2006). The available data suggest that LSD1 is recruited by VP16 from its partner (Zhou et al., 2010). Once ICP0 is made, additional proteins (e.g. CD4, CLOCK, etc) are recruited to enhance genes expression (Kalamvoki and Roizman 2010).

All α gene promoters contain the response elements required for the binding of the VP16/Oct1/HCF1/LSD1 complex(Mackem and Roizman, 1982, Pellett et al., 1985, Kristie and Roizman, 1987, McKnight et al., 1987, Kristie and Roizman, 1988) and hence they are predicted to be derepressed. At the same time the observation that the synthesis of ICP4, ICP22, ICP27, and ICP47 but not that of ICP0 depends on the recruitment of CLOCK (Kalamvoki and Roizman 2010) suggests that the interactions of ICP4, ICP22, IC27 and ICP47 promoters with the VP16/Oct1/HCF1/LSD1 complex are necessary but not sufficient for their expression. The data also predict that there may be some fundamental differences in the response elements present in the promoter of ICP0 as compared to those of other α genes.

Expression of β and γ genes

The promoters of β and γ genes lack the response elements for binding of VP16/Oct1/HCF1/LSD1 complex. Numerous studies, too numerous to cite here, focused on finding group-specific response elements in β and γ genes to no avail (Reviewed in Roizman et al., 2013). The available data again, too numerous to cite here, indicate that derepression of α genes does not ipso facto result in the expression of all viral genes. Numerous studies have pointed to ICP0 as the key element necessary but not sufficient for the expression of all viral genes.

ICP0 is the epitome of a multifunctional protein. It binds numerous proteins and performs multiple functions throughout the replicative cycle of the virus (Reviewed in Roizman et al., 2013). It resides in the nucleus during the first 6 to 7 h after infection and then mysteriously disappears from the nucleus and appears in the cytoplasm. The duration of the sojourn in the nucleus is depended on the amount of DNA introduced into the cells along with the virus (Lopez et al., 2001; Kalamvoki and Roizman, 2008). Relevant to the expression of β and γ genes are two functions. In the order of discovery, ICP0 acts as an E3 ubiquitin ligase. In combination with the UbCH5A ubiquitin conjugating enzyme it degrades PML and SP100. (Boutell et al., 2002, Gu and Roizman, 2003) A consequence of the degradation of PML and SP100 is the dispersal of the constituents of the ND10 bodies). What remains in their place are host and viral proteins recruited by α proteins. They form the nucleus of the replication compartments in which viral DNA is transcribed and replicated (Reviewed in Roizman et al., 2013). The second function of ICP0 is to bind CoREST and displace HDAC1 or 2 from to HDAC/CoREST/LSD1/REST (HCLR) complex (Gu et al., 2005, Gu and Roizman, 2007). The known functions of the HCLR complex are to repress neuronal genes in non-neuronal cells (Ballas and Mandel, 2005). REST is a highly postranslationally modified protein with repressor binding sits at both ends of the protein. It binds a somewhat degenerate response element (RE1). On displacement of HDAC1 by ICP0 the complex falls apart and its components are translocated to the cytoplasm (Gu et al., 2005, Gu and Roizman, 2007)

Both degradation of PML and disassembly of HCLR complex have been linked to the derepression and expression of β and γ genes and their functions are not clearly separable (Lopez et al.,

Please cite this article as: Roizman, B., Zhou, G., The 3 facets of regulation of herpes simplex virus gene expression: A critical inquiry. Virology (2015), http://dx.doi.org/10.1016/j.virol.2015.02.036