Virus Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Virus Research

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

Review

Recent advances in preclinical model systems for papillomaviruses

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ARTICLE INFO

Article history:
Received 3 December 2016
Accepted 5 December 2016
Available online xxx

Keywords:
Animal papillomavirus models
Innate immune responses to PV infections
BPV
CRPV
CPV
MmuPV1
Vaccine and immunotherapeutics for PV infections
in vivo PV viral function
Codon-modified viral genes

ABSTRACT

Preclinical model systems to study multiple features of the papillomavirus life cycle have greatly aided our understanding of Human Papillomavirus (HPV) biology, disease progression and treatments. The challenge to studying HPV in hosts is that HPV along with most PVs are both species and tissue restricted. Thus, fundamental properties of HPV viral proteins can be assessed in specialized cell culture systems but host responses that involve innate immunity and host restriction factors requires preclinical surrogate models. Fortunately, there are several well-characterized and new animal models of papillomavirus infections that are available to the PV research community. Old models that continue to have value include canine, bovine and rabbit PV models and new rodent models are in place to better assess host-virus interactions. Questions arise as to the strengths and weaknesses of animal PV models for HPV disease and how accurately these preclinical models predict malignant progression, vaccine efficacy and therapeutic control of HPV-associated disease. In this review, we examine current preclinical models and highlight the strengths and weaknesses of the various models as well as provide an update on new opportunities to study the numerous unknowns that persist in the HPV research field.

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http://dx.doi.org/10.1016/j.virusres.2016.12.004
0168-1702/

1. Introduction

Papillomaviruses are a diverse group of DNA viruses that cause epithelial lesions of skin and mucosa (https://pave.niaid.nih.gov/). These viruses are found ubiquitously in the animal kingdom and contribute substantial morbidity and mortality in the form of cancers of the anogenital and oral mucosa. Oral cancers associated with human papillomavirus type 16 (HPV16) are on the increase, and the effectiveness of current prophylactic vaccines against several high-risk HPV types (hrHPV) on HPV cancerous disease await final confirmation after several decades of data collection. Animal papillomaviruses are now characterized in many mammalian species and in several preclinical laboratory models (reviewed in (Rector and Van, 2013)). In particular, rodent, lagomorph, canine, bovine and equine papillomaviruses have been studied as surrogates for HPV disease, diagnosis, treatment and vaccine assessment (reviewed in Peh et al., 2002). New PV models in the laboratory mouse system are available and continue to advance our knowledge of mucosal infections in clinically important sites.

Significant advances in understanding papillomavirus biology were obtained in early studies on bovine, rabbit and dog models. From these initial studies we gained important fundamental knowledge on viral gene function, tissue tropism, cancer progression, vaccine efficacy and therapeutics. More recent models include multi-mammate rats, and a mouse papillomavirus that can infect laboratory mouse strains. Much is still to be learned regarding the role of innate immunity on control (or lack of control) during the early stages of infection, the molecular basis of tissue tropism and site-specific targeting of PV infections at non-lymphoid tissues of the anogenital and oral mucosa. In this review we discuss some recent advances in preclinical papillomavirus models that continue to improve our understanding of papillomavirus biology, virus life cycle and therapeutic control of these important human viral pathogens.

2. Preclinical models (in vivo)

2.1. Bovine papillomavirus and cattle

Bovine papillomavirus type 1 (BPV-1) produces fibropapillomas on cattle causes tumors in rodents and transforms fibroblasts in culture (Lancaster et al., 1976, 1979; Dvoretzky et al., 1980). It was the first papillomavirus genome to be sequenced (Fig. 1) (Chen et al., 1982) and the BPVs are important preclinical models to study cutaneous and mucosal infections and PV-associated cancers. BPV-1-induced papillomas can be large and produced substantial quantities of infectious virions that were subsequently used to study viral structure transforming function in cell culture and viral protein and gene function (Baker et al., 1991; Booy et al., 1998; Meischke, 1979; Rabson et al., 1986; DiMaio et al., 1982; Baker and Howley, 1987). In addition, further studies with the bovine papillomaviruses revealed many different types which demonstrated different tissue specificities (Campo, 1987; Rector and Van Ranst, 2013). BPV-2 and BPV-4 were found to be associated with bladder and alimentary canal cancers respectively (Campo et al., 1992; Gaukroger et al., 1993) and are important models to study PV infections and environmental co-carcinogens (Campo, 1987). Few researchers today use this model as costs and management of cattle in academic and industrial institutions are significant and other smaller preclinical models are available. Important contributions from this virus are particularly noted in the discovery of a small hydrophobic protein known as E5 (Fig. 1) (Schiller et al., 1986; DiMaio et al., 1986) which is also found in many human papillomaviruses (HPVs) and that has transforming function (reviewed in DiMaio and Petti, 2013), host immune modulating activity (Ashrafi et al., 2006), and can activate various cellular growth factors (DiMaio and Petti, 2013; Conrad et al., 1993; Finbow et al., 1991). Another interesting model has arisen from the observation that BPV-1 can cause equine sarcoids in horses (Chambers et al., 2003). This equine model is amenable to testing immunotherapeutic approaches given that these infections are difficult to treat yet retain BPV-1 viral antigens as foreign targets for T-cell based strategies (Carr et al., 2001; Chambers et al., 2003; Bogaert et al., 2015).

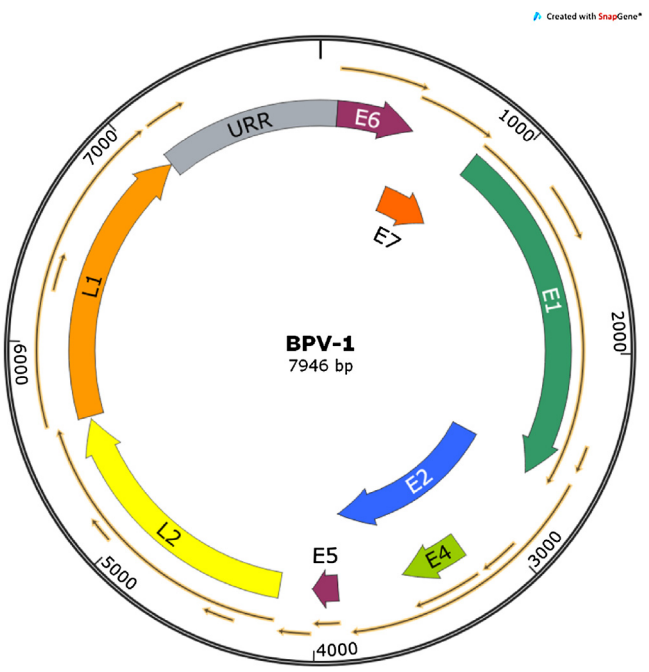

Fig. 1. BPV-1 genome.

2.1.1. Opportunities for ongoing and new studies with the bovine PV models

- Assess mechanisms of tissue restriction of various different bovine PV types. Determine the viral components that lead to a "relaxed" tissue restriction of BPV-1/2 in which both epithelial and fibroblastic cells respond to infection in vivo.
- Assess efficacy of vaccines targeting multiple types with different anatomical locations in single outbred animals.
- Determine the molecular and cellular mechanisms of BPV-associated cancer in the co-presence of plant-derived co-carcinogens.
- Test immunotherapeutic approaches to cure/prevent persistent and recalcitrant lesions caused by BPV-1 infection of horses.

2.2. Canine papillomavirus and dogs

Canine oral papillomavirus (COPV) or CPV1 (Fig. 2) was the first canine PV studied and has relevance to clinically important HPV infections due to the mucosotropic nature of this virus (Chambers and Evans, 1959; Watrach et al., 1970; Delius, et al., 1994). The model was used to assess virus-like particle (VLP) vaccines and DNA-based prophylactic vaccines (Suzich et al., 1995; Kirnbauer et al., 1996; Moore et al., 2003) as well as natural host immunity to infections that predominantly regress over time (Nicholls et al., 2001). An intriguing observation arose when COPV genome was sequenced in which a non-coding region of 1500 bp was found to be located between the E2 and L2 gene (Delius et al., 1994). The evolutionary origins of this sequence and its potential function in the viral life cycle remain unknown (Bravo and Felez-Sanchez, 2015). More

Please cite this article in press as: Christensen, N.D., et al., Recent advances in preclinical model systems for papillomaviruses. Virus Res. (2016), http://dx.doi.org/10.1016/j.virusres.2016.12.004