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History of Papillomavirus Research

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2.1. Introduction

Papillomavirus research has passed through several phases. The field began slowly with the experimental transmission of human and animal warts prior to 1930. Greater interest in these viruses was stimulated in the 1930s by the demonstration that filtered extracts from cutaneous papillomas of wild cottontail rabbits could induce lesions with malignant potential in cottontail and domestic rabbits. Although investigations in the 1930s and 1940s were limited to in vivo studies in outbred rabbits, many principles of papillomavirus biology were established by observations made during this period. The availability of infectious extracts permitted the reproducible induction of lesions whose natural history could be followed or be experimentally modified. Interest in papillomaviruses diminished during the 1950s and 1960s. This change was attributable to several factors, including the inability of papillomaviruses to propagate in culture at a time when the life-cycle and transforming activity of other oncogenic viruses could be studied in vitro, permitting rapid advances in molecular understanding of these processes in the more tractable systems. In addition, human papillomaviruses (HPV) were believed to have limited medical importance because the conditions they induced were thought to be limited to benign lesions with little or no potential for malignant progression. The advent of molecular cloning during the 1970s led to a resurgence in papillomavirus research. As in other areas of biology, this technical revolution was critical to progress in the investigation of papillomaviruses. The unlimited availability of wild-type and mutant viral genomes made it possible to study the function of viral genes and their products, to use viral sequences as molecular probes to detect papillomavirus sequences in tissue, and to identify and molecularly clone new viral genotypes. Application of these molecular techniques led to the identification of HPV as the necessary infectious cause of a major public health problem, cervical cancer. These studies also provided insight into the pathogenesis of HPV-induced disease, established new paradigms for cellular transformation by viral genes, and identified candidate antigens for protection against papillomavirus infection.

There have been excellent reviews relevant to the history of papillomavirus research. They include those for tumor viruses in general (Gross, 1983); for DNA tumor viruses (Grodzicker and Hopkins, 1981); for animal papillomaviruses (Lancaster and Olson, 1982); for cottontail rabbit papillomavirus (Breitburd et al., 1997; Kreider and Bartlett, 1981; Syverton, 1952); for HPV (Rowson and Mahy, 1967); for HPV in epidermodysplasia verruciformis (Orth, 1986); and for HPV in genital neoplasia (zur Hausen and de Villiers, 1994). This chapter highlights research advances from the 1930s through the early 1990s. Prior to the mid-1970s, most observations were first made in animal papillomavirus systems. Since then, the analysis of HPVs and the diseases they induce has produced many key observations, although experimental animal papillomavirus systems have also continued to yield important insights.

2.2. The 1930s and 1940s: Biology of the Shope Papillomavirus and Other Animal Papillomaviruses

Papillomaviruses were the second class of viruses, after retroviruses, shown to induce malignant tumors (Shope, 1933). As such, the Shope papillomavirus, which is now designated the cottontail rabbit papillomavirus (CRPV), became an important experimental model of viral tumorigenesis. Not only did infectious extracts induce benign papillomas in cottontail and domestic rabbits, but some of the benign lesions progressed to squamous cell cancers, the first demonstration that a mammalian virus could cause a malignant solid tumor (Rous and Beard, 1935; Syverton, 1952; Syverton and Berry, 1935). It was also found that some papillomas regressed, while others persisted without progression. A causal relationship between persistence of a papilloma and the risk of malignant progression was inferred, as the carcinoma developed at the site of the papilloma and malignant tumors still expressed viral antigens. In addition, if a lesion regressed, the site of the former lesion was no longer at risk for carcinoma development. However, it was not clear whether the virus in the papilloma played a specific role in progression or if the virus was required for maintenance of the carcinoma. Another poorly understood feature of the malignant tumors was that the virus was “masked,” which meant that infectious virus could not be recovered from them (Kidd and Rous, 1940). Such uncertainties should not obscure the fact that the observations made with CRPV established many salient biological characteristics of papillomavirus infection that were subsequently found to be relevant to HPV infection and carcinogenesis.

In the decade following the description of CRPV, prominent themes of CRPV research involved efforts to understand the basis for the outcome of infection and to modify the frequency with which the virus induced papillomas or carcinomas. The combination of CRPV and coal tar greatly increased the rate at which carcinomas developed (Rous, 1938; 1944), thus establishing the concept that certain environmental exposures could promote the likelihood of progression. It was also found that the development of papillomas was associated with the induction of

serum neutralizing antibodies and with concomitant resistance to CRPV challenge at other cutaneous sites (Kidd et al., 1936; Shope, 1933). Furthermore, systemic immunization with papilloma suspensions could, without establishing cutaneous infection, induce serum-neutralizing antibodies and protect against high dose cutaneous viral challenge (Shope, 1937). These early studies therefore laid the foundation for the belief that induction of humoral immunity could form the basis of a preventive vaccine against papillomaviruses. These results also showed that distinct processes mediated resistance to *de novo* infection and regression of established papillomas, as neutralizing antibodies did not influence regression. Importantly, spontaneous regression appeared to be an immune phenomenon in that it usually affected most or all papillomas on the rabbit.

Early research also established the exquisitely specific host range of papillomaviruses. CRPV induced papillomas in rabbits only when nongenital skin was inoculated; genital skin and various mucous membranes were resistant (Parsons and Kidd, 1936a; Shope, 1933). When a second papillomavirus, the rabbit oral papillomavirus (ROPV), was isolated from spontaneous papillomas in the mouth of domestic rabbits (Parsons and Kidd, 1936b, 1943), it was shown to induce papillomas only to the oral mucosa and to lack oncogenic potential. CRPV and ROPV were shown to be distinct viruses, as animals infected by one virus developed resistance to the homologous virus while remaining susceptible to the heterologous one. Furthermore, species other than rabbits were resistant to infection by CRPV and ROPV. These findings indicated that these viruses are remarkably restricted in the range of host species that they infect and that papillomaviruses may exploit distinct ecological niches by infecting various subsets of stratified squamous epithelia. These observations also showed that more than one virus may infect a single host species, and that protection against infection by one papillomavirus may not confer protection against another.

Experimental studies with the canine oral papillomavirus (COPV) also emphasized the narrow host range of papillomaviruses. Experimental transmission of oral papillomas in dogs had been reported in the late 19th century (M'Fadyean and Hobday, 1898) with material obtained from an outbreak in foxhound puppies (Penberthy, 1898). The filterable nature of the etiological agent was demonstrated in the early 1930s (DeMonbreun and Goodpasture, 1932; Findlay, 1930). The papillomas induced by COPV uniformly regressed spontaneously, dogs were the only species susceptible to COPV infection, and inoculation of epithelial sites in the dog other than the oral mucous membranes failed to induce papillomas. COPV and ROPV were clearly distinct viruses, as neither induced oral lesions in the other host species.

Bovine papillomavirus type 1 (BPV1) was also identified during this period (Creech, 1929; Magalhaes, 1920). In its natural host, BPV1 induced fibropapillomas (consisting of both dermal fibroblasts and epidermal epithelial cells), in contrast to the strictly epithelial lesions (papillomas) characteristic of other papillomaviruses, including HPV. Although BPV1 produced the characteristic epithelial changes seen with other papillomaviruses, its ability to induce morphologic changes in the underlying dermis was a reflection of the wider host range

of BPV1. However, the significance of this feature does not appear to have been appreciated until the early 1950s, with the observation that BPV1 could induce a benign fibroblastic tumor in horses (Olson and Cook, 1951). The experimental lesions closely resembled those of equine sarcoid, a naturally occurring condition of horses subsequently found to contain BPV DNA (Lancaster et al., 1977).

2.3. The 1950s and 1960s: Cell Differentiation and Virus Replication

The development of tissue culture techniques in the 1940s and 1950s did not lead to the successful in vitro propagation of papillomaviruses. By contrast, the life-cycle and transforming activity of polyoma virus and SV40 virus, which had been discovered in the late 1950s (Stewart et al., 1958; Sweet and Hilleman, 1960), could be studied in monolayer cultures. The latter viruses, therefore, became the most popular DNA tumor viruses to study, leading to remarkable advances in understanding their molecular biology and impact on cells. Interest in papillomaviruses waned in the 1950s and 1960s largely because they continued to be less tractable to tissue culture analysis and because human papillomaviruses were not thought to be agents of medically important disease. During this period, papillomaviruses were classified as belonging to the same virus family as polyoma and SV40 (the *papovaviridae*), as the papillomavirus capsid and genome were both structurally similar to, but larger than, those of polyoma and SV40 (Crawford, 1969; Stone et al., 1959; Williams et al., 1961).

Despite the shift in focus to other tumor viruses, there were some notable advances in papillomavirus biology in the 1950s and 1960s. The development of fluorescent antibody microscopy and improvements in electron microscopy made it possible to examine viral structural antigens and virus particles in papillomas. The analysis of CRPV papillomas showed that structural antigen and particles were limited to the nuclei of differentiated keratinocytes in the upper layers of the lesion and that infectious virus was also found in these layers (Moore et al., 1959; Noyes, 1959; Noyes and Mellors, 1957). The chronic nature of papillomas had implied that the virus would be present in the basal cells of lesions, as most epithelial cell division occurs in basal cells. Therefore, the lack of virus particles in the basal cells of papillomas led to the inference that the virus in the basal cells was present in an immature form. The results therefore implied that papillomavirus replication was closely tied to the differentiation process of stratified squamous epithelial cells, an insight which provided a likely explanation for the inability to propagate papillomaviruses in monolayer cultures. In fact, suitable multilayer differentiated culture systems were not developed and applied to the in vitro study of papillomaviruses until many years later (McCance et al., 1988; Dollard et al., 1992; Meyers et al., 1992).

These observations with virions were followed by the demonstration that DNA from CRPV papillomas could induce papillomas that resembled those induced by CRPV virions (Ito and Evans, 1961). This technique was also used to establish

that the viral DNA was present in a transplantable carcinoma (VX7) that had been induced by CRPV, as DNA extracts from the carcinoma could induce papillomas, although the extracts did not contain infectious virus (Ito and Evans, 1965). The data, therefore, indicated that a non-encapsidated form of the viral genome was present in the transplantable tumor, and provided the first example of an oncogene transferable as naked DNA.

During this period, additional evidence was developed that regression in rabbit papillomas was an immunologically mediated event that required more than neutralizing antibodies or was independent of them. The frequency of regression was decreased when immunosuppression was induced with methylprednisolone (McMichael, 1967). Conversely, the rate of regression was increased when rabbits with papillomas were immunized systemically with minced papilloma tissue containing intact cells, although regression could not be induced by passive transfer of serum to rabbits with persistent papillomas (Evans et al., 1962). In addition, the resistance of regressor rabbits to papilloma formation was shown to be qualitatively different from that of naïve, virus-immune, and papilloma-bearing rabbits. This difference was shown first by making short-term cultures of skin explants from rabbits with each type of history, infecting the explants with CRPV, and then transferring them as an autograft to the rabbit from which each had been taken. Autographs did not form papillomas in regressor rabbits, while they did form papillomas in naïve, virus-immune, and papilloma-bearing rabbits (Kreider, 1963). Analogous results were obtained when regressor rabbits or rabbits with persistent papillomas were inoculated with extracts containing CRPV DNA. Although the CRPV DNA could produce papillomas in rabbits with persistent papillomas and neutralizing antibodies, the viral DNA was ineffective in regressor rabbits (Evans and Ito, 1966). In addition to confirming that the presence of neutralizing antibodies was not sufficient to induce regression, these studies supported the conclusion that regression was mediated by nonhumoral, cellular immunity.

2.4. The 1970s to the Early 1990s: Viral Genetics and the Emergence of HPV as a Medically Important Virus

Molecular cloning and related techniques developed in the mid-1970s partially overcame the experimental limitations to studying papillomaviruses, leading to renewed interest in these viruses and to a wealth of new information about them. During the late 1970s and early 1980s, papillomavirus research followed two main themes: experimentally oriented studies of animal papillomaviruses, especially BPV1, and more clinically oriented studies of HPVs. By the second half of the 1980s, clinical and experimental aspects of HPVs became predominant, following the recognition of their medical importance.

BPV1 had two attractive properties. First, there was a readily renewable source of virions, as BPV1 could be serially propagated *in vivo* from extracts of the large lesions it induced in cattle. Second, building on earlier studies of BPV1 with

primary cell cultures (Black et al., 1963; Thomas et al., 1964), BPV1 was found to induce morphologic transformation and focus formation of established tissue culture cell lines, such as the mouse C127 and NIH 3T3 cell lines (Dvoretzky et al., 1980). In contrast, CRPV and the HPVs known in 1980 did not display this activity. The ability of BPV1 to transform cultured nonepithelial cells is related to its wider *in vivo* host range. As noted earlier, BPV1 is the prototype for a class of animal papillomaviruses that induce fibropapillomas in their natural host. This broad host range at the cellular level presumably endows BPV1 with the ability to induce nonepithelial lesions in heterologous hosts (Friedmann et al., 1963; Olson and Cook, 1951).

The availability of a bio-assay for BPV1 in established cells, combined with the ability to molecularly clone and mutate the viral genome, made it possible to study the genetics of this virus. The experimental importance of BPV1 attracted the interest of molecular biologists and resulted in BPV1 being the first papillomavirus genome to be completely sequenced (Chen et al., 1982), with those of HPV1 (Danos et al., 1982, 1983) HPV6 (Schwarz et al., 1983), and CRPV (Danos et al., 1984; Giri et al., 1985) completed shortly thereafter. These data showed that distinct papillomaviruses share a similar genetic organization and possess considerable sequence homology. When combined with transcription analysis (Heilman et al., 1982; Engel et al., 1983), the viral genome could be divided into three segments: a noncoding region, a region coding for the nonstructural ("early" [E]) genes, and a region coding for the two viral capsid proteins ("late" [L]). In contrast to earlier expectations, the organization of the papillomavirus genome was distinct from that of SV40 and polyoma, and there was almost no sequence homology between papillomaviruses and polyomaviruses. For example, the papillomavirus E and L genes are transcribed from the same strand, while those of SV40 and polyoma are transcribed from opposite strands. Such differences eventually led to papillomaviruses being designated a separate virus family.

The genetics of BPV1 was studied largely by examining two parameters: rodent cell transformation and the generation of episomal viral DNA. These latter studies were stimulated by the surprising finding that cells transformed by BPV1 contained multiple episomal copies of the viral genome (Law et al., 1981), in contrast to cells transformed by SV40 or adenoviruses, which contained exclusively integrated viral DNA. Cells transformed by BPV1 appeared to be the *in vitro* counterpart to the underlying fibroblastic portion of BPV1 fibropapillomas in the natural host or the nonepithelial lesions in heterologous hosts. As in nonepithelial lesions in the animal, the L genes were not expressed in tissue culture and did not contribute to transformation or to viral DNA replication. Genetic analysis identified two genes, E5 and E6, with a direct role in morphologic transformation (Groff and Lancaster, 1986; Schiller et al., 1984; Schiller et al., 1986; Yang et al., 1985). E5 was found to transform cells by activating receptor tyrosine kinases (Martin et al., 1989) via the direct activation of PDGF β -receptors (Petti et al., 1991), with a possible contribution by its binding to a component of the vacuolar H^+ -ATPase (Goldstein et al., 1991). The E2 gene was found to regulate the expression of other viral E genes, by trans-activation

following the binding of E2 protein to cognate binding sites located mainly in the viral noncoding region (Androphy et al., 1987; Spalholz et al., 1985). E1 was shown to be an ATP-dependent helicase required for the replication of viral DNA (Clertant and Seif, 1984; Lusk and Botchan, 1985; Yang et al., 1993; Seo et al., 1993), with E2 having a key ancillary role in viral DNA replication (Mohr et al., 1990; Ustav and Stenlund, 1991; Yang et al., 1991).

Infection of the esophagus by BPV4 represented an important animal papillomavirus model developed in the 1970s (Jarrett et al., 1978). As with CRPV, BPV4 causes benign tumors that sometimes progress to invasive cancer. Unlike CRPV, the BPV4 lesions were located at mucosal, not cutaneous surfaces. The development of esophageal cancer in the infected cattle was related to their eating bracken fern, which contained a carcinogen. This was a natural situation where a nonviral environmental exposure contributed to the carcinogenic progression of a papillomavirus infection. The esophageal cancers did not contain the viral genome, in contrast to the benign lesions (Campo et al., 1985). This form of progression therefore operates via a hit-and-run mechanism, which is unusual for viral-induced cancers in general, and for other papillomavirus-associated cancers in particular.

The study of HPVs also reached a major turning point. Transmission of warts from one individual to another had been achieved in the late 19th century, and the viral etiology of genital and nongenital warts was shown in the first part of the 20th century (Ciuffo, 1907; Serra, 1924; Ullmann, 1923; Variot, 1894). Furthermore, nongenital warts could be induced experimentally by extracts from genital warts and from laryngeal papillomas, suggesting that the responsible viruses might be identical. A particularly noteworthy advance came from the recognition, based on molecular analysis, that there were several HPV genotypes. In one situation, it was recognized that several HPV genotypes caused nongenital cutaneous warts (Gissmann et al., 1977; Orth et al., 1977). In another, it was noted that distinct papillomavirus genotypes were associated with the skin lesions of epidermodysplasia verruciformis (EV) (Orth et al., 1978b), a rare susceptibility to widespread cutaneous warts. Still other HPV types were responsible for genital warts (Gissmann and zur Hausen, 1980; Orth et al., 1978a). These findings implied that there were a large number of HPV genotypes, as has been borne out by subsequent studies.

Studies on EV conducted by Orth and colleagues uncovered a treasure trove of interesting properties of HPVs (Orth, 1978b, 1979, 1986). Some skin lesions in EV progress to squamous cell carcinoma. Analysis of the malignant tumors indicated that the vast majority of them contained either of two closely related HPV genotypes (HPV5 or HPV8), although many HPV genotypes were present in benign EV lesions. These findings represented the first clear evidence that HPV was involved in human cancer. A second important conclusion was that some HPV genotypes had greater malignant potential than others. Although the benign EV lesions were present on both covered and exposed areas of the body, almost all the malignant tumors were found on exposed areas. This observation implied that while HPV infection with HPV5 or HPV8 might be necessary for

skin cancer, progression to invasive cancer also required exposure of the lesion to ultraviolet light, a carcinogen known to be active as an initiator and a promoter in skin cancer.

The study of the genital-mucosal HPVs, primarily by zur Hausen and colleagues, led to findings of even greater medical importance. It was noted in the mid-1970s that the histologic appearance of cervical dysplasia, the cellular precursor to cervical cancer, resembled that of viral papillomas (Meisels and Fortin, 1976). This observation, combined with other evidence, led to the suggestion that HPV infection may play a role in cervical carcinogenesis (Meisels and Morin, 1981; zur Hausen et al., 1981). The first genital-mucosal HPV types to be isolated were HPV6 and HPV11 (de Villiers et al., 1981; Gissmann et al., 1983). Although these viruses were present in a high proportion of benign genital warts, related sequences were found in only a minority (~10%) of cervical cancers. A major breakthrough in revealing a role of HPV in cervical cancer came from the identification and molecular cloning of HPV16 (Durst et al., 1983) and HPV18 (Boshart et al., 1984) DNA, two genotypes only distantly related to HPV6/11. It was soon determined that the majority of cervical cancers contained DNA that hybridized under stringent conditions to probes from HPV16 or HPV18. Under less stringent conditions, an even higher proportion of cervical cancers hybridized to these viral DNAs. The findings therefore implicated HPV in a common human cancer. The potential public health implications of these findings gave new prominence to HPV research and attracted many new investigators, particularly medical epidemiologists, to the field. Although some epidemiological studies in the mid-1980s identified major differences in the incidence of HPV16 in cervical cancers, compared with low grade cervical lesions or normal cervixes (McCance et al., 1985), others did not. These variable results, which resulted from a combination of false-positive and false-negative HPV DNA data, were overcome by the development of PCR primers for the reliable detection of small quantities of genital-mucosal HPV DNA in cervical smears (Resnick et al., 1990; van den Brule et al., 1990), leading to cervical HPV infection being recognized as the predominant risk factor for cervical cancer and its precursor lesions (Schiffman, 1992), although HPV infection is not sufficient for cervical cancer. Further studies indicated that virtually all cases of cervical cancer were initiated by infection with high-risk HPV types (Walboomers et al., 1999).

A series of observations about the oncogenes of HPV16 and 18 and the biochemical activities of their encoded proteins also had an enormous impact on the field. It was shown initially in cervical cancer cell lines that the viral DNA was often integrated, in a deleted form, into the host genome, in contrast to the episomal nature of the viral genome in benign lesions (Schwarz et al., 1985). Although integration was relatively random with respect to the host DNA, integration was not random with respect to the viral genome. In the tumors, the noncoding region of the genome along with the E6 and E7 genes were preferentially retained, and both genes were expressed in the tumors (Schwarz et al., 1985; Smotkin and Wettstein, 1986; Schneider-Gadicke and Schwarz, 1986). These results provided a strong clue that E6 and E7 were major transforming

genes of the virus. The expression of E6 and E7 also appeared to be necessary for cervical cancer cell lines to maintain their transformed phenotype (Thierry and Yaniv, 1987; von Knebel Doeberitz et al., 1988; Hwang et al., 1993).

HPV6 and HPV11 were almost never found alone in cervical cancer, which gave rise to the notion that these genital-mucosal HPVs were “low-risk” types, while those HPVs that were found regularly in cervical cancer, such as HPV16 and HPV18, were “high-risk” types. Although low-risk and high-risk HPVs were able to stimulate human keratinocyte growth, the high-risk HPVs possessed additional biological properties, including the ability to immortalize primary human keratinocytes (Durst et al., 1987; Pirisi et al., 1987; Schlegel et al., 1988; Woodworth et al., 1988, 1989; Kaur and McDougall, 1989). Furthermore, efficient keratinocyte immortalization could be attributed to a cooperative activity between high-risk E6 and high-risk E7 (Hawley-Nelson et al., 1989; Munger et al., 1989). Consistent with the notion that HPV infection is necessary, but not sufficient, for malignant progression, human keratinocytes immortalized by HPV16 DNA were not tumorigenic in experimental animals, but malignant transformation could be induced by continued passage or transfer of an activated *ras* oncogene (DiPaolo et al., 1989; Pecoraro et al., 1991). In transgenic mice, co-expression of HPV-16 E6 and E7 in epithelial cells induced papillomas, epithelial hyperplasia, and carcinoma (Lambert et al., 1993; Arbeit et al., 1994).

Insight into the mechanisms underlying these properties of high-risk E6 and E7 genes came from identification of biochemical activities displayed by their protein products. First, it was shown that high-risk E7, but not low-risk E7, bound and inactivated the pRb tumor suppressor protein (Dyson et al., 1989; Munger et al., 1989; Gage et al., 1990; Chellappan et al., 1992), a property originally identified in the adenovirus E1A protein and also in the SV40 large T antigen. It was then determined that high-risk E6, but not low-risk E6, formed a complex with the p53 tumor suppressor protein (Werness et al., 1990), which is also targeted by the other small DNA tumor viruses. p53 activity was reduced because E6 binding led to p53 degradation via a ubiquitin-dependent process involving the formation of a trimolecular complex that in addition to E6 and p53 included E6AP, a newly identified protein that was found to be a ubiquitin ligase (Scheffner et al., 1990, 1993). These results were correlated with the finding that the p53 and Rb genes were wild type, rather than mutated, in human cervical cancer cell lines associated with high-risk HPV, while they were frequently mutated in HPV-negative lines (Scheffner et al., 1991; Wrede et al., 1991).

Thus, by the early 1990s, HPVs had been identified as the etiologic agent for cervical cancer, and the continued expression of E6 and E7 in cancer cells was recognized, as were some of the main biochemical activities of the viral oncoproteins. The combination of the medical importance of HPVs and their mechanisms of cell transformation attracted widespread interest, from basic scientists to clinicians. It is noteworthy that the achievements of papillomavirus research from the 1970s through the early 1990s occurred despite the inability to propagate the virus in culture. Research during this period set the stage for many subsequent important advances, including the use of HPV DNA testing in cervical

cancer screening, the identification of HPV in normal individuals and in a wider spectrum of cancers, the efforts to interfere with HPV infection by vaccination and other modalities, the recognition that most viral genes, including E6 and E7, are multifunctional, and the development of in vitro assays for papillomavirus replication. Many of these advances are described in detail elsewhere in this volume.

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