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Small DNA Tumor Viruses: Large Contributors to Biomedical Sciences

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Abstract

Studies of the small DNA tumor viruses (the polyomaviruses, the adenoviruses and the papillomaviruses) have led to fundamental discoveries that have advanced our understanding of basic mammalian cell molecular biology processes such as transcription and DNA replication, uncovered pathways and genes often perturbed in human cancer, and identified bona fide human cancer viruses. In this article we examine the many contributions that have come from the small DNA tumor virus field and provide a recounting of some of the major landmark.

Keywords

SV40; polyoma; HPV; papillomavirus; BPV; p53

Viral oncology can trace its beginnings to observations made during the early part of the 20th century when the transmissibility of avian leukemia was first described by Ellermann in Denmark in 1908 and the transmissibility of an avian sarcoma in chickens was described by Rous in 1911 (Ellermann and Bang, 1908; Rous, 1911). These findings were, however, not fully appreciated at the time, and their full impact on virology and medicine was not recognized until the 1950s with the identification of murine tumor viruses that could be studied experimentally in a controlled setting. In this context, the 1966 Nobel Prize in Medicine that recognized the work of Peyton Rous that first identified that a filterable agent from a sarcoma could induce tumors in chickens was not awarded until nearly 50 years after the initial discovery.

The first evidence of mammalian tumor viruses came in the 1930s with the work of Richard Shope who published several papers demonstrating cell free transmission of tumors in rabbits. The first studies involved fibromatous tumors found in the footpads of wild cottontail rabbits that could be transmitted by injecting cell free extracts into either wild or domestic rabbits. The relevant virus, referred to as the Shope fibroma virus, is now known to be a pox virus. Other studies by Shope in this time period demonstrated that cutaneous papillomatosis in wild cottontail rabbits could also be transmitted by cell free extracts. In a number of cases, these benign papillomas would progress spontaneously into squamous cell carcinomas in infected domestic or cottontail rabbits (Rous and Beard, 1935; Shope and Hurst, 1933). The field of

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viral oncology, however, was still not fully appreciated until the early 1950s with the discovery of the murine leukemia viruses by Ludwig Gross (Gross, 1951) and of the mouse polyoma virus by Gross, Stewart, and Eddy (Gross, 1953; Stewart, 1953).

The discovery of tumor viruses in mice made it possible for researchers to explore the role of viruses as cancer- inducing agents though the medium of well controlled experiments with some expectation that such studies would provide insights into the mechanisms underlying human cancer and the possibility that some proportion of human tumors might even have a viral etiology. The Special Viral Cancer Program at the National Cancer Institute in the late 1960s grew from this intense interest in viral oncology and the hope that human tumor viruses would be identified through its efforts. It is now recognized that between 15–20% of human cancers can be directly associated with infection by certain viruses.

This special edition of *Virology* is focused on the small DNA tumor viruses, which include the polyomaviruses, the adenoviruses, and the papillomaviruses. It should be noted that the polyomaviruses and papillomaviruses were originally classified together as different genera of the papovaviruses (pa=papillomavirus; po=polyomavirus; and va=vacuolating virus for SV40) because of similar morphology by electron microscopy. Indeed it was not until genome comparison studies of the late 1970s and early 1980s that the polyomaviruses and papillomaviruses were recognized as distinct families of viruses. It should also be noted that the small DNA viruses do not include all of the types of DNA viruses that are associated with naturally occurring tumors. Other DNA viruses associated with human cancers are the herpesviruses (Epstein-Barr Virus and Kaposi's Sarcoma Herpesvirus) and the hepadnaviruses (Hepatitis B virus).

The focus by tumor virologists on the above-noted small DNA tumor viruses can be traced back forty years to the first DNA tumor virus meeting that was held at the Cold Spring Harbor Laboratories in August, 1969, the first year that part of the annual Tumor Virus meeting was devoted to reports of research on the DNA tumor viruses. The organizers of this first, annual meeting on the DNA tumor viruses were Carel Mulder, Joe Sambrook and James D. Watson. Most of the abstracts from that meeting involved SV40, polyomavirus and adenovirus.[1] During the same year Watson initiated a focus on tumor virus research at the Cold Spring Harbor Laboratories with the recruitment of Joe Sambrook and other young virologists, who began to work on SV40 and the adenoviruses. The papillomaviruses did not become a regular feature of this meeting until the late 1970s following the successful cloning of papilloma viral genomes by recombinant DNA techniques.

Many of the most important developments in modern molecular biology derive from studies in viral oncology. Although this article will focus on the discoveries that have come from studies of the small DNA tumor viruses, it should be noted that the RNA tumor viruses led to the discovery of reverse transcriptase by Howard Temin and David Baltimore and the concept of oncogenes. Table 1 provides a list of major discoveries made at the hands of an analysis of small DNA viruses. In addition to the discoveries of the first papillomavirus (CRPV) in 1933, the murine polyomavirus in 1953 and SV40 in 1960, Table 1 provides an accounting of landmark discoveries that can be attributed to the DNA tumor viruses.

The DNA tumor viruses provided vital tools for molecular biologists to study complex nuclear events in mammalian cells in the 1970s and the 1980s. Indeed, they continue to do so. Studies of these small DNA viruses were fundamental in the development of recombinant DNA technology. SV40 DNA was the first viral genome for which a restriction endonuclease map

[1]We are grateful to Terry Grodzicker and Clare Clark at the Cold Spring Harbor Laboratories for providing us a copy of the abstract book of the 1969 Tumor Virus Meeting held at Cold Spring Harbor.

was developed and the first to be sequenced in its entirety. Such studies were soon followed by the completion of sequencing and gene mapping of murine polyomavirus and the human adenoviruses.

A major focus of the small DNA tumor virus field was and still is cellular transformation. Studies from Fried using a temperature sensitive murine polyomavirus established that the virus encodes a gene responsible for the initiation and maintenance of a transformed phenotype (Fried, 1965). More relevant still, transformation studies with the polyomaviruses have identified genes and pathways that have proven critical in human cancer. The murine polyomavirus encodes three different transforming proteins (Small, middle and large T antigens) and among the targets of these viral oncogenes are Src kinase, PI3 kinase, shc, and protein phosphatase 2A. Perhaps the major contribution of the small DNA viruses to an understanding of human cancer has been the recognition that some of the viral oncogenes encoded by these viruses are transforming because they bind and functionally perturb certain established tumor suppressor genes. This was first shown for the E1A oncoprotein of adenovirus and the retinoblastoma gene product (pRB) (Whyte et al., 1988), followed soon thereafter by studies with SV40 large T-antigen (DeCaprio et al., 1988) and HPV16 E7 (Dyson et al., 1989).

A discovery that also emerged from studies of the small DNA tumor viruses and that is the most revealing of a mechanism underlying much of human cancer development was that of p53 in 1979 as a protein bound tightly to SV40 large T-antigen (Lane and Crawford, 1979; Linzer and Levine, 1979). The significance of the interaction of p53 with SV40 large T was not appreciated until the late 1980s when it became clear that, like pRB, p53 is also a tumor suppressor gene, and its function is compromised by binding to T Ag. Moreover, like pRB, p53 is also targeted by oncoproteins encoded by other small DNA viruses. The 55kDa product encoded by the adenovirus E1B gene (Sarnow et al., 1982) and the high-risk HPV E6 proteins (Werness, Levine, and Howley, 1990) both bind and compromise p53 function. Thus a penetrant theme among the small DNA tumor viruses is that key activities of some of their oncoproteins result from an ability to target and inactivate certain cellular tumor suppressor gene products. The viral oncoproteins of these small DNA viruses target many other cellular proteins and perturb numerous other homeostatic signal transduction pathways on the way to eliciting a neoplastic phenotype, as is well documented in the other articles in this volume.

Another major discovery relevant to cellular transformation was the finding that certain oncogene products cooperate with one another in eliciting a transformed phenotype. This observation emerged initially from studies with the adenoviruses showing a transformation requirement for E1A as well as E1B (Van den Elsen, Houweling, and Van der Eb, 1983). The notion of cooperating oncogenes was subsequently extended to cellular oncogenes, such as myc and ras (Land, Parada, and Weinberg, 1983). Another observation that emerged from studies of the adenoviruses and directly relevant to cancer was the finding that Ad E1A contributes to tumorigenesis by the down modulation of expression of the major histocompatibility genes (Schrier et al., 1983). This implied that suppression of an immune response was needed before tumorigenesis could occur. Moreover, work from the Nevins laboratory led to the identification of the E2F family of transcription factors critical to cell cycle regulation (Kovesdi, Reichel, and Nevins, 1986). Subsequent studies in the field identified the E2F factors as the targets of pRB (and the related p107 and p130 pocket proteins) (Dyson, 1998).

In addition to observations that revealed roles in cancer development for certain tumor suppressing and oncogenes and signal; transduction pathways in which they participate, fundamental discoveries regarding the nature and mechanisms underlying basic mammalian cell processes such as transcription and DNA replication emerged from studies of these viruses.

Among these include the discovery of mRNA splicing with adenovirus (Berget, Moore, and Sharp, 1977; Chow et al., 1977). Studies of SV40 and polyomavirus transcription also led to the identification of DNA-based transcriptional enhancer elements (Banerji, Rusconi, and Schaffner, 1981; Benoist and Chambon, 1981), and these, in turn, led to the identification of specific DNA binding transcription factors (Dynan and Tjian, 1983). Studies of SV40 transcription also led to the elucidation of polyadenylation signals (Fitzgerald and Shenk, 1981). The first In vitro mammalian DNA replication systems was established for adenovirus DNA (Challberg and Kelly, 1979), subsequently for SV40 DNA, and eventually for the papillomavirus DNAs (Li and Kelly, 1984; Yang et al., 1991). These studies have contributed to the identification and functional understanding of a number of mammalian cell DNA replication factors. In addition, studies of SV40 large T-antigen led to the identification of protein nuclear localization and trafficking sequences (Kalderon et al., 1984; Lanford and Butel, 1984).

Major contributions to understanding the nature of in vivo protein degradation and the ubiquitin pathway came from studies of the high risk HPVs associated with human cancer. Studies with the E6 and p53 led to the identification p53 as the first mammalian substrate of the ubiquitin-dependent polypeptide degradation system (Scheffner et al., 1990) and the characterization of E6AP as the first mammalian ubiquitin E3 protein-ligase (Scheffner et al., 1993). Subsequent studies, including those with the adenoviruses (Querido et al., 1997), established ubiquitin-mediated proteolysis as a process regularly employed by tumor viruses.

Certain small DNA tumor viruses cause disease in man. Indeed, the 2008 Nobel Prize in Medicine recognized Harald zur Hausen for his discovery of specific HPVs associated with human cervical cancer. Specifically using non-stringent hybridization conditions, he and his colleagues identified two new HPV types (HPV16 and HPV18) in cervical cancer specimens and demonstrated their association with carcinomas and precancerous lesions of the cervix (Boshart et al., 1984; Durst et al., 1983). The same cervical cancer- associated HPVs are also associated other anogenital cancers and with approximately 20% of upper airway cancers. Another subset of HPV (the beta genus), members of which were first identified and studied by Gerard Orth and Stephania Jablonska in patients with epidermodysplasia verruciformis (Orth, 2005), may also have a role in skin cancers. If they are etiologic agents in these cancers, their role may involve a hit and run mechanism, since the viral DNAs are not generally found in these tumors.

Although SV40 and the human polyomaviruses have been important models for studying cellular transformation, their potential role in human cancers has been less clear. There have been periodic reports dating back to the 1970s claiming the presence of SV40 DNA in a variety of different human cancers, including osteosarcomas, mesotheliomas, pancreatic tumors and brain tumors. This has been a very controversial area and one that has received considerable scrutiny from investigators in the field and by the National Cancer Institute (Poulin and DeCaprio, 2006; Shah, 2007). The recent identification of a new human polyomavirus in Merkel cell cancers, however, appears to be a solid candidate for behaving as a human cancer virus (Feng et al., 2008).

Methods such a single DNA molecule sequencing and high density SNP arrays for readily detecting very small amounts of viral DNA integrated into host cell genomes now exist. With their application to searches for new DNA tumor viruses in human tumors, other new, small DNA human tumor- associated viruses might be discovered in the years ahead.

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Table 1

Landmark Discoveries Involving the Small DNA Tumor Viruses

YEAR	Discovery	Key References
1933	First mammalian tumor virus (CRPV)	(Shope and Hurst, 1933)
1953	Discovery of the murine polyomavirus	(Gross, 1953; Stewart, 1953)
1960	Discovery of SV40	(Sweet and Hilleman, 1960)
1965	Oncogene addiction (Polyomavirus ts mutants)	(Fried, 1965)
1973	First restriction map of a virus (SV40)	(Danna, Sack, and Nathans, 1973)
1977	RNA splicing	(Berget, Moore, and Sharp, 1977; Chow et al., 1977)
1978	First animal virus genome sequence (SV40)	(Fiers et al., 1978; Reddy et al., 1978)
1979	First mammalian viral vector (SV40)	(Hamer and Leder, 1979; Mulligan, Howard, and Berg, 1979)
1979	Discovery of p53	(Lane and Crawford, 1979; Linzer and Levine, 1979)
1979	In vitro viral DNA replication systems leading to identification of mammalian DNA replication factors	(Challberg and Kelly, 1979)
1981	Identification of polyadenylation signal	(Fitzgerald and Shenk, 1981)
1981	Transcriptional enhancers	(Banerji, Rusconi, and Schaffner, 1981; Benoist and Chambon, 1981)
1983	Identification of Src as a target of PyMT	(Courtneidge and Smith, 1983)
1983	Discovery of specific HPV types in cervical cancer	(Boshart et al., 1984; Durst et al., 1983)
1983	Identification of specific transcriptional factors (SP1)	(Dynan and Tjian, 1983)
1983	Viral down modulation of Class I histocompatibility genes	(Schrier et al., 1983)
1983	Oncogene cooperation (Ad E1A and E1B)	(Van den Elsen, Houweling, and Van der Eb, 1983)
1984	Nuclear trafficking sequences	(Kalderon et al., 1984; Lanford and Butel, 1984)
1986	Discovery of E2F	(Kovesdi, Reichel, and Nevins, 1986)
1988	Discovery that DNA TV oncogenes target cellular tumor suppressor genes (pRB)	(DeCaprio et al., 1988; Whyte et al., 1988)
1989	Development of Virus Like Particles for DNA viruses (Py)	(Salunke, Caspar, and Garcea, 1989)
1990	Identification of protein phosphatase 2A as a target of the polyomavirus small t antigens	(Pallas et al., 1990; Walter et al., 1990)
1993	Identification of the first mammalian E3 ubiquitin-protein ligase (E6AP)	(Scheffner et al., 1993)
2006	FDA approved HPV VLP based preventive vaccine	(Koutsky et al., 2002)
2008	Discovery of the Merkel Cell Polyomavirus	(Feng et al., 2008)