Chapter 17

Interaction Between Viral Proteins and Caretakers — Polyomavirus as a Model

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Additional information is available at the end of the chapter

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1. Introduction

DNA repair plays an essential barrier against birth of a precancerous cell [1]. In nature history of cancer, one important characteristic is genomic instability [2]. Among tumor suppressor genes (TSG), the functions of caretakers including DNA repair genes are crucial for cellular genomic integrity. They prevent the mutation of other TSG, e.g. gatekeepers and landscapers [3]. Virueses are always more complicated than human understanding. They not only direct host replication machineries but also interact with a wide variety of cellular proteins. In the past decade, some viruses have been reported to hijack DNA repair proteins and/or collaborate DNA damage response (DDR) which favor their own life cycle or induce carcinogenesis of host cells [4, 5].

Several members of *Polyomaviridae*, a family of circular double-stranded DNA tumor viruses, induces multiple tumors in animal [6]. The family includes some famous animal viruses, i.e. simian virus 40 (SV40) and murine polyomavirus (MPyV), and twelve not very well-characterized human polyomaviruses, e.g. JC virus (JCV), BK virus (BKV), merkle cell polyomavirus (MCV), KIV, WUV, etc. SV40 contributes to numerous pioneer discoveries, including eukaryotic DNA replication, alternative splicing, the interaction/inactivation of tumor suppressor genes etc., and serves as a paradigm in molecular biology [7, 8]. Furthermore, SV40 is suspected as an emergent human pathogen and a co-carcinogen of human mesothelioma which is due to its contamination of poliovirus vaccine [9]. The relationship of SV40 and human cancer has been comprehensively evaluated by the International Agency for Research on Cancer (IARC) in 2012. Human MCV has been identified as a probably human carcinogen and associated with a highly aggressive human skin carcinoma, merkel cell carcinoma (MCC) [10]. Due to the high prevalence of human polyomaviruses and life-long persistent infection in human [11, 12], the interaction between polyomaviruses and host proteins still is the barren areas to be explored.

In this chapter, we will briefly review the recent development regarding the interaction between polyomavirus proteins and cellular caretakers. This chapter will depict the roles of polyomaviruses in deregulating DNA repair, genomic stability and provide a valuable information for the studies of DNA repair affected by viral proteins.

2. Family polyomavirudae

2.1. Genome strutures and gene products of polyomaviruses

The genomes of polyomaviruses, about 5.0~5.4 kb, contain early, late and non-coding regulatory regions (Figure. 1A). The large tumor antigen (LT Ag) and small tumor antigen (ST Ag) are produced by alternative splicing from the early transcript. They have common N terminal but unique C terminal sequences that lead them to interact with different host proteins [13]. The sequence of LT Ag contains the Dna J domain, for heat shock protein 70 binding, and retinoblastoma (pRb) and p53 protein binding domains. The ST Ag sequence contains common N terminal region (Dna J domain) and unique C terminal region which bears binding site for protein phosphatase 2A (PP2A) [14]. However, the number and structure of alternative transcripts are different among polyomaviruses. Besides LT and ST Ags, SV40 also produces 17 kT Ag; MPyV has middle T and TT Ag, JCV has T'135, T'136 and T'165; BKV has trunc T, MCV has 57kT splicing variants. Most studies focus on their LT Ags which play essencial roles for viral replication and transformation. ST Ags are known to be the helper for transformation [15]. The late region codes for structural proteins VP1, VP2 and VP3. Agnoprotein, the smallest one, is also produced from late region. It plays roles in viral relication, transcription and virion synthesis [16].

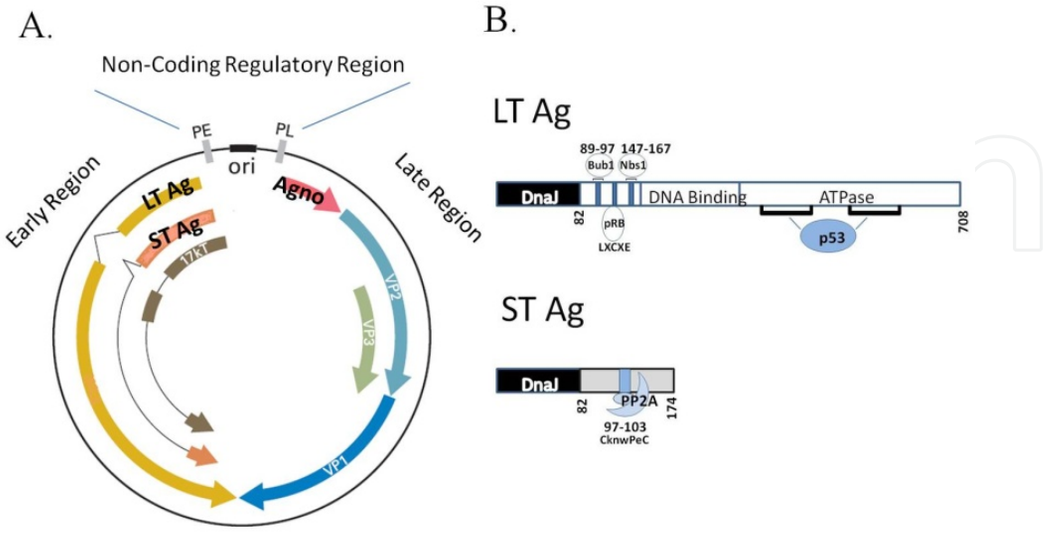

Figure 1. A. The genome structure of SV40 (5243 bp), the representative polyomavirus. B. The LT and ST Ags of SV40. The binding regions of major caretakers are indicated.

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2.2. Polyomaviruses and human cancers

MCV is a new human polyomavirus discovered in 2008 and is found to be clonally integrated into the genome of MCC at a frequence of ~80% [10]. Merkel cells reside in the basal layers of skin and express dual epithelial/neuroendocrine phenotypic markers. MCC is a rare but highly aggressive skin cancer which typically affects elderly and immunocompromised individuals [17]. In 2013, IARC declared that MCV is probably carcinogenic to humans (Group 2A). It is the human polyomavirus which has most tightly association with human cancer so far. Most of the MCV genomes found in MCC carry various C-terminal truncation in LT Ag, while the virus preserves full-length of ST open reading frame. The tumor derived LT Ag is a specific signature for MCV [18].

Another two human polyomaviruses, JCV and BKV, were intially isolated from immunocompromised patients in 1971 [19, 20]. JCV caused progressive multifocal leukoencephalopathy in AIDS patients. BKV led to nephropathy or hemorrhagic cystitis. Importantly, they are oncogenic when inoculated into newborn rodents. These viruses persist in multiple tissues of host for life-long infection. Epidemiological studies found that they are widespread and common in human population [11, 12]. The seropositive rates of JCV and BKV in normal adults can be as high as 72%-98% [21]. Until 2007, only these two human polyomaviruses were known to infect human beings. Currently, several new human polyomaviruses have been detected [10, 22]. Seropoistive rates by using newer method to avoid cross reaction are 9% (SV40), 82% (BKV), 39% (JCV), 42% (MCV), 55% (KIV) and 69% (WUV) [23]. Some studies explored the relationship of BKV and JCV in human cancers [6, 21, 24]. For example, by using polymerase chain reaction (PCR) and immunohistochemistry (IHC) etc. methods, the DNA and LT Ag of neurotropic JCV have been detected with high prevalence in different types of neural cancers [25-27]. Its DNA and LT Ag could be also detected in lung and colon cancers [21, 27-32]. JCV and BKV are highly suspective as human carcinogens. In 2013, IARC evaluated and declared that JCV and BKV are possibly carcinogenic to human as Group 2B carcinogens.

SV40 was discovered in 1960 and long suspected as human emergent virus [33]. The natural host of SV40 is rhesus macaue. However, SV40 contaminated poliovirus vaccines were used to inoculate approximately 100 million peoples in the United States and countless more throughout the world between 1955 and 1963. SV40 DNA had been detected in many types of cancer by PCR-based assays [34, 35]. The PCR-based assays, including false positive by contamination and crossreaction with JCV and BKV ect., raised many debates and controversy about SV40 in human tumors. High seropositve of SV40 were found by crossreaction with JCV and BKV in human serum. Epidemiological studies showed no trend of increased number of cancer cases related to persons who received SV40-contaminated vaccine. The prevalence of SV40 was studied by using high specific assay (virus like particles assay ect.) and found that only 1.0%-1.6% seropositive of SV40 in individuals born before 1963 [36]. However, the longstanding controversies were discussed by IARC group and at present SV40 is classified to Group 3, not classifiable as to its carcinogenicity to humans [37].

3. Anti-cancer barriers

3.1. DNA repair caretakers

Myriad of exogenous and endogenous DNA damaging events threaten cellular genetic information every moment. Cells have to invest abundant proteins for repairing DNA mutation and maintaining their genomic integrity to prevent the birth of cancer [1, 38, 39]. DNA repair systems are crucial and evolutionally conserved [40]. Several DNA repair systems are responsible for dealing with different kinds of DNA damages. Nucleotide excise repair (NER) removes UV-induced cyclopyrimidine dimer (CPD), pyrimidine-6,4-pyrimidone photoproducts (6-4 PP) and polyaromatic hydrocarbons (PAH) bulky adducts; base excision repair (BER) repairs the modified bases (e.g. 8-oxy-guanine) and abasic sites etc. causing by endogenous physical reactions; mismatch repair (MMR) deals with the mismatch nucleotides which raises from error of DNA polymerase. These pathways comprise recognition, excision and polymerization processes to repair the DNA lesions. Non homologous end join (NHEJ) and homologous recombination repair (HRR) are mechanisms to repair double strand breakages (DSBs) induced by exogenous irradiation, e.g. X-rays and anti-tumor agents. These cellular DNA repair pathways are clearly reviewed elsewhere [41]. The main caretaking systems which polyomaviruses interact and interfere are described as follows.

3.1.1. NER caretakers

The repairosome for NER embraces 20-30 distinct proteins to remove CPD, 6-4 PP and bulky adducts. Major effectors which include protein products of XPA-XPG genes, have defect in xeroderma pigmentosum *(XP)* patients who are extremely prone to skin cancer [42]. There are two initial subpathways for NER DNA damage recognition, the transcription coupled NER (TC-NER) and global genomic NER (GG-NER) (Figure 2A). The TC-NER recognizes the DNA damages on transcribed templates. The GG-NER first globally screens the disrupted base pairing by GG-NER specific factor, XPC-hHR23B. These two subpathways differ only in the initial steps of DNA damage recognition. Following XPC-hHR23B GG-NER initiator, the DDB1/DDB2 heterodimer (XPE) recognize and bind the UV lesions to initiate GG-NER cascade. Differently, TC-NER required CSB and CSA, TC-NER specific factor, for blocking elongating PolII on DNA lesions. After lesions recognition, the subsequent stages of two subpathways are identical. The XPB 3′-5′ and XPD 5′-3′ helicases, subunits of TFIIH, unwind the double strand and form DNA bubble. The single-stranded binding protein, replication protein A (RPA), stabilizes the open intermediates. Then, the endonuclease team, XPG and XPF, respectively cleave the 3′ and 5′ of opened damaged strand, excise 24-32-base oligonucleotide to remove the injury. The DNA polymerase δ and/or ε then fill and ligate the gap. The tumor suppressor p53, dual function as gatekeeper and caretaker, plays a pivotal role in NER [43]. Most obviously, the promoters of XPC and DDB2 contain the p53 responsive elements and are regulated transcriptionally by p53 [44]. The functions of NER effector/regulator which are targeted by polyomaviruses are listed on Table 1.

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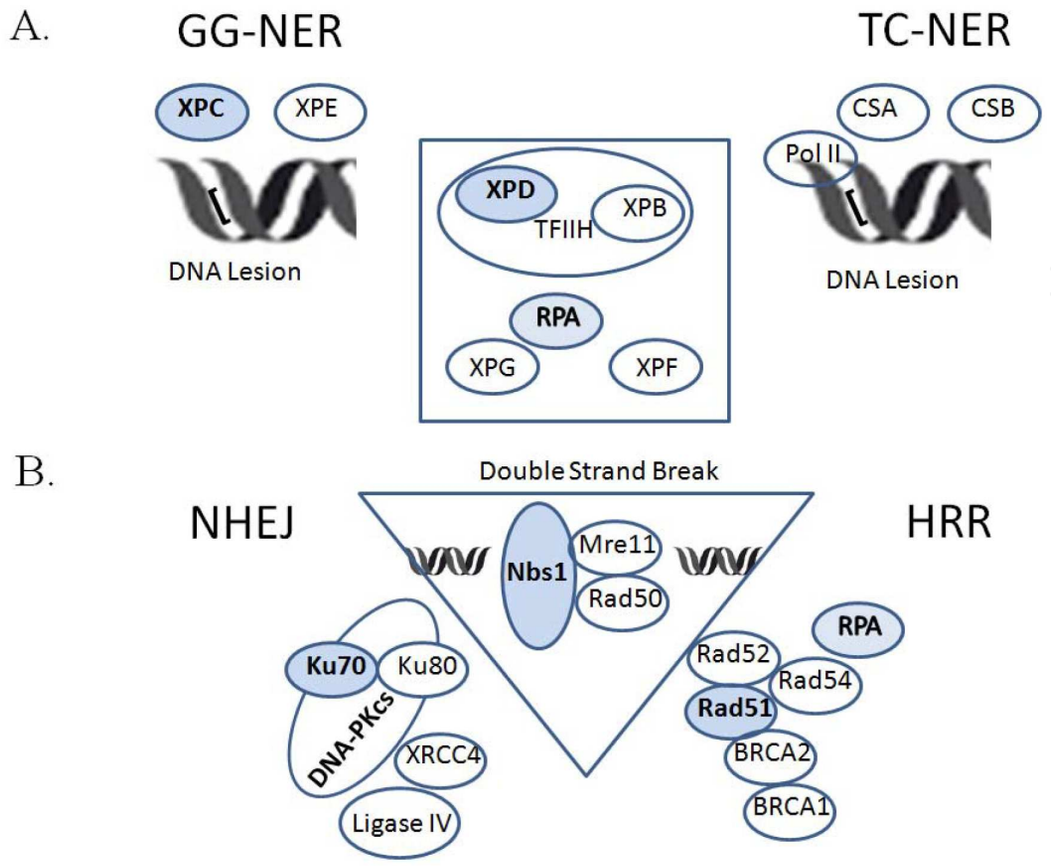

Figure 2. A. Effectors of NER. The common XP components, which participated in both GG-NER and TC-NER, are indicated by square. B. Effectors involved in DSBs repair. MRN complex, which participates in both HRR and NHEJ, is indicated by reverse triangle. The effectors which are targeted by polyomaviruses are colored by light blue.

3.1.2. HRR and NHEJ caretakers

DSBs are serious threats to genomic integrity. The HRR and NHEJ pathways contribute to genetic stability by removing a wide range of DSBs through error-free or error-prone reaction. HRR is error-free homologous recombination-based repair which occurs in S/G2/M phases and uses sister chromatids as the template to repair DSBs. Differently, DSBs in G1/S phase trigger NHEJ for error-prone repair. When DSBs occur, the signal transducing kinase, ataxia telangiectasia mutated (ATM), is autophosphorylated at S1981. It further phosphorylates p53, breast cancer 1 (BRCA1) and Nijmegen breakage syndrome 1 (Nbs1) and so on. Nbs1 and BRCA1 are defected on hereditary disorders which loss genomic stability through problems of DNA repair pathways and can directly contribute to human malignancy.

After ATM activation, it phosphorylates H2AX, also indicated as γ-H2AX (the marker of DNA damage), to form DNA damage foci in the flanking chromatin [45]. The Mre11-Rad50-Nbs1 (MRN) complex is then recruited to DSBs and promotes bridging of the DNA ends. MRN complex, as sensor, participates both in NHEJ and HR pathways (Figure 2B). If cells are in G1/S phase, Ku70/80 hetrodimers, the NHEJ specific caretakers, form complex with DNA-PKcs as a docking site for other NHEJ proteins, XRCC4 and ligase 4, for further end processing and

ligation [46]. For HRR, the single strand binding protein RPA facilitates the assembly. Rad51 recombinase, together with Rad52 and Rad54, catalyzes strand-exchange reaction and interacts with BRCA2/ BRCA1. The functions of HRR/NHEJ effector/regulator which are targeted by polyomaviruses are listed on Table 1.

Caretaking systems	Caretakers	Functions	Refs
Nucleotide Excision Repair (NER)	RPA	Single-strand binding protein	41,42
	XPC	CPD, bulky DNA adduct recognition	41,42
	XPD	5'-3' DNA helicase	41,41
	p53	NER Regulator [Regulate NER and MMR (transcription dependent); NER, BER, MMR, NHEJ and HRR (transcription independent)]	43,44
Homologous Recombination Repair (HRR)	Nbs1	Member of Mre11/Rad50/Nbs1 complex (DSB repair complex)	41,46
	Rad51	Recombinase for HRR (bacterial RecA homolog)	41,46
Non-Homologous End Join (NHEJ)	Ku70/Ku80 hetrodimer	Form complex with DNA protein kinase (DNA-PKcs)	41,46
	PP2A	dephosphorylation of Ku, DNA-PKcs and γ-H2Ax; Centrosome cycle	74,77
Mismatch repair (MMR)	hMSH3, hMSH6	Mismatch, insertion/deletion recognition	41
	hPMS1, hMLH1	form heterodimer	41
Spindle Assembly Checkpoint (SAC)	Bub1	Serine/Threonine-protein kinase For proper chromosome segregation	47
Interstrand Cross-Linked Repair (ICL)	FancD2	Caretaker in ICL	63

Table 1. The functions of caretakers which are targeted by polyomavirual proteins

3.1.3. MMR caretakers

The recognition proteins of DNA mismatch pairing and single base loops are hMSH2/6 heterodimer, whereas insertion/deletion loops detection are performed by hMSH2/3 hetrodimer. The hMLH1/hPMS2 are recruited to mismatch sites by interacting with MSH complex. Additional MMR factors search for a signal that identify the wrong strand and resynthesis the excised one. These include RPA, proliferating cell nuclear antigen (PCNA), RFC, exonuclease 1 and endonuclease FEN1. MMR components also interact with NER and recombination.

3.2. Spindle Assembly Checkpoints (SAC) caretakers

Caretaker genes encode proteins that stabilize the genome including DNA repair factors, cell-cycle checkpoints. Cell-cycle checkpoints stop cell-cycle progression when DNA damages occur. Caretakers do not directly control cell birth or cell death but rather control the rate of mutations of other genes, including gatekeeper genes. Except important G1 and G2 check-

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points, the SAC [47] and centrosome cycle [48] regulate chromosome distribution. To ensure the fidelity of chromosome segregation, the SAC blocks the ubiquitin ligase activity of anaphase-promoting complex (APC)-Cdc20 in response to a sister chromatid which is not properly attached to the mitotic spindle through kinectochore. The components of SAC including Mad1, Mad2, Bub3, Bub1 and Mps1 play crucial roles to guard and initiate sister chromatides segreagation. Among them, Bub1 is a serine/theronine kinase and inhibits Cdc20 by phosphorylation [49]. To ensure equal distribution of sister chromatids, the centrosome has to duplicate before mitosis and serves as the spindle poles during mitosis. Aurora A, a serine/threonine kinases, is associated with centrosomes and localized at the centrosome just prior to the onset of mitosis. The activity of aurora A is regulated by phosphorlyation and proteasomal degradation [48].

Retinoblastoma protein (pRB), a pocket protein, is a famouse cell-cycle moleculer brake. Through phosporylation cascade of cyclin/cyclin dependent kinase, pRB is activated to release E2F for entering into S phase. It directly controls cell birth and is considered as a gatekeeper gene. LT Ags of polyomaviruses also contain the LXCXE sequences and interact with pRB gatekeeper to deregulate cell cycle. This important interaction between polyomaviruses and host is also indicated in Figure 1B. The functions of other effectors in genomic stability which are targeted by polyomaviruses are listed on Table 1.

4. Interaction between SV40 viral antigens and DNA repair proteins

Despite SV40 is not a significant human oncogenic virus, it is a powerful model system for our understanding of the molecular interactions between virus and host. Those are not only important in virology and also in cell and cancer biology. In addition to the well-established effects of SV40 LT Ag in deregulating the cell cycle, this viral protein plays an important role in the development of genomic instability. LT Ag of SV40 is DNA damage regent and is enough to induce DDR in cells [50]. Furthermore, LT Ag binds and inactivates p53 and pRb, which play a significant role in their transformation activity. Although, SV 40 LT Ag simultaneously inactivates the pRb, a gatekeeper TGS, and p53, the gatekeeper/caretaker TGS; however, the studies indicated that complete transformation of human cells requires the additional inactivation of PP2A, the gatekeeper/caretaker TSG, by ST Ag [51, 52]. SV40 cellular targets which involve in genomic instability are described below.

4.1. SV40 LT Ag and p53, Nbs1, Bub1

LT Ag of SV40 interacts with many important cellular proteins. It has served as a useful paradigm for understanding cell transformation. In 1979, scientists reported the discovery of a 53 kDa protein that was present in human and mouse cells [8, 53-57]. The 53 kDa protein was discovered because it bound to the LT Ag in SV40 infected cells. Now, we know that the tumor suppressor TP53 is the most frequently altered gene in human.[58] It plays super star roles on cancer biology in past 30 years [58]. It functions as a transcription factor and regulates hundred of genes through its DNA binding domain. Now, this cellular partner of LT Ag in SV40, p53,

is called "genome guardian". It receives upstream signals (DNA damage, cell stress and oncogene activation) and directs downstream cellular responses (cell cycle arrest, DNA repair and apoptosis) to maintain the genome integrity.

Virus	Viral proteins	Cellular targets	Impaired DNA repair	Refs
SV40	LT Ag	p53	NER, BER, MMR, NHEJ and HRR	53-57
		Bub1	Mitotic Spindle checkpoint	50
		Nbs1	HRR , NHEJ	65
		MRN foci decreased	HRR, NHEJ	65,66
		FancD2 relocalized	HRR, ICL (FancD2/BRCA1 foci)	61
		PML	HRR (Rad51/Nbs1/PML foci)	61
		p53	GG-NER	67
		hMSH3,hMLH1 etc.	MMR	68
	ST Ag	PP2A	NHEJ, centrosome cycle	74-77
MPyV	OBD* in LT Ag	RPA	NER, HRR, NHEJ	92
	ST, Middle T	PP2A	?	94

*: Origin binding domain, residues 264-420 in LT Ag of MPyV

Table 2. Cellular caretakers targeted by animal polyomaviral antigens

DNA damage elicits ATM/ATR activation and p53 phosphorylation. The negative regulator of p53, MdM2, is then displaced. The expression level and transcriptional activity of p53 are increased [59]. Through its transcriptional regulation function, activated p53 regulates NER and MMR. However, p53 can through its transcription-independent process to modulate NER, BER, MMR, NHEJ and HRR [43]. For NER, p53 has essential functions through its transcription-dependent and transcription-independent roles. The NER effectors, XPC and DDB2, are transcriptionally regulated by p53. There are p53 responsive elements in their promoter regions [44]. p53 also modulates the enzymatic activity of XPD and XPB helicases by its transcription-independent function. p53 recruits the histone acetylase p300 to NER sites to acetylate histone H3, thereby through epigenetic regulation relaxing the chromatin and enhancing NER. p53 functions as a 'molecular node' in DDR and plays the pivotal role in NER [43]. There are bipartite p53 binding regions in SV40 LT Ag which are located around the C' terminal ATPase domain (Fig. 1B). SV40 LT Ag binds and inactivates p53. The crystal structure of SV40 LT Ag and p53 complex revealed that LT Ag occupies the whole p53 DNA-binding domain and interferes with formation of p53 tetramer [60].

Gjoerup's groups reported that LT Ag of SV40 deregulated multiple DDR and repair pathways [61]. Individual domains of LT are connected to different subcomponents of the DDR and repair machinery. LT and 17 T bind Bub1 through residues 89-97 [50](Figure 1B). Bub1 is a

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member of mitotic SAC and plays an important role in safeguarding the genome. Bub1 kinase delays anaphase progression if microtubules haven't attached to kinetochores on metaphase. Bub1 mutation results in chromosoml instability (CIN) and aneuploidy in human cancer [62]. SV40 LT Ag attacks the genomic integrity by binding to Bub1 [50]. It doesn't require the viral replication origin of genome. LT Ag alone can induce DDR and Chk1/Chk2 activation. Through Bub1 binding, LT Ag induces significant tetraploidy. It is suggested that p53 inactivation is important for cell survival in tetraploidy. SV40 LT Ag via Bub1 binding induces γ−H2AX and 53BP1 foci, the hallmarks of DDR.

Gjoerup's groups further found that LT Ag induces a distinct set of foci, H2AX/53BP1 in the G1 phase, Fanconi anemia group D2 protein (FancD2)/BRCA1 or Rad51/Nbs1/ promyelocytic leukemia protein (PML) in G2/S phases [61]. LT Ag induces activation of the FancD2 by relocalizing it into foci on chromatin. LT Ag also induces distinct foci of the HRR recombinase Rad51, which are colocalized with Nbs1 and PML. FancD2 protein, a caretaker protein involved in repair of DNA interstrand cross-links (ICLs), is monoubiquitinated in response to DNA damage, resulting in its localization to nuclear foci with BRCA1 and BRCA2 which involved in HRR. Foci of FancD2 and BRCA1 are mainly found in S/G2 and likely connected with a replication stress response [63].

SV40 LT Ag also induces distinct foci of the HRR recombinase Rad51. It colocalizes with PML and Rad51. It targets PML, a transcription factor and tumor suppressor, to Rad51 HRR recombinase and results in inefficient HRR [64].

SV40 LT also interacts with Nbs1, another protein of MRN complex, through its residues 147-167 [65] (Figure 1B). MRN complex forms at DSBs DNA damage foci. Interaction of Nbs1 by SV40 LT Ag impaired both HRR and NHEJ. Nbs1 is a multifunction protein that contributes to proper DNA replication and the maintenance of genomic stability. Nbs1 suppresses rereplication of cellular DNA and SV40 origin-containing replicons. Interaction of SV40 LT Ag and Nbs1 also results in enhancing the yield of new SV40 genomes during viral DNA replication [65].

In irradiated human fibroblast, the presence of SV40 LT Ag disturbs the formation of nuclear trimeric MRN DNA-repair foci. This MRN complex involves in NHEJ and HRR. These strongly elucidate interference of DNA repair by SV40 LT Ag [66].

In addition to the effect of SV40 LT Ag in disrupting HRR and NHEJ, SV40 also impairs GG-NER of CPD, most likely because inactivation of p53 by its LT Ag [67]. SV40 LT Ag also been reported to interfere MMR. In SV40 LT expressing cells, the MMR activity (for G:T, A:C, G:G) was deficient, and MMR genes (hMSH3, hMSH6, and hPMS1) were expressed at a low level and hMLH1 was mutated and/or deleted. This MMR deficiency also contributes to genetic instability [68].

4.2. SV40 ST Ag and PP2A

In 1990, SV40 ST Ag and MPyV ST and middle T Ag have been demonstrated to form stable complexes with PP2A [69]. PP2A, the important cellular target of SV40 ST Ag, is a serine/threonine phosphatase. Complexly regulated PP2A has been identified as a multiple function

tumor suppressor gene. It plays as a negative regulator for PI3K/AKT, MAPK, Wnt, NF-κB, PKC pathways to control cell growth, division and survival [70]. Inhibition of PP2A activity is essential for cell transformation [71]. SV40 ST Ag, through its residues 97-103 CknwPeC, binds PP2A [72]. This viral protein displaces regulatory subunit B of PP2A to form ST-PP2A/AC complex with structural subunit A and catalytic subunit C heterodimer [14]. Mutiple functions of PP2A were disclosed through interaction and inhibition by SV40 ST Ag. For example, it disrupts cell adhesion and cytoskeletal dynamics which is linked to loss of cell polarity, increased cell motility and invasiveness [73].

Significantly, PP2A, a SV40 ST-targeted tumor suppressor gene, also plays a critical role in DNA repair and genome stability. Inactivation of PP2A via SV40 ST Ag represses cellular NHER repair activity. By using SV40 ST Ag as PP2A inhibitor, PP2A had been demonstrated to promote NHEJ by dephosphorylation of Ku70 and DNA-PKcs, and forms Ku/DNA-PKcs complex to bind to DNA ends [74] (Figure 3). This is a novel mechanism of NHEJ promotion by PP2A through direct dephosphorylation of Ku and DNA-PKcs. The involvement of PP2A to repair DSBs contributes to maintenance of genetic stability. On the other hand, PP2A also facilitates DSBs repair through dephosphorylate γ-H2AX to recruit effectors of NHEJ [75]. Cells overexpressing SV40 ST Ag can't form organized centrosome and alters centrosome cycles [76]. PP2A interacts with Aurora A which regulates centrosome dynamic [77]. The abnormal centrosome cycles in cells overexpressing SV40 ST Ag may be due to inactivation of PP2A. SV40 ST Ag disrupts the caretaker roles of PP2A. Taken these studies together, SV40 ST Ag via PP2A binding, probably impairs chromosomal stability through different mechanisms.

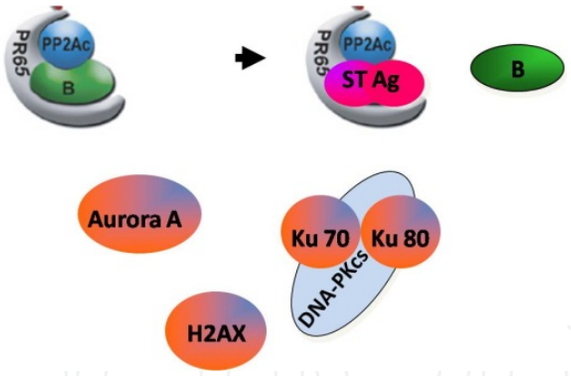

Figure 3. ST Ags of SV40 and JCV disrupt the PP2A holoenzyme. The ST Ag competes with regulatory subunit B of PP2A and inactivates its phosphatase activity. The substrates of PP2A which is involved in genomic stability are indicated.

5. MCV LT Ags, DDR and DNA repair

MCV is the human polyomavirus which is most tightly associated with human cancer. Recently, Li et al. found that the interesting differences between LT Ags of SV40 and MCV. Full length MCV LT Ag, through its C-terminal domain, activates ATR and Chk1 pathway via

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$p53^{s15}$ activation. It induces DDR in host genome (SV 40 LT Ag activates a DDR through ATM and ATR pathway but inhibits p53 function). MCV LT Ag arrests cell cycle. It, just as antitumor effect, inhibites cell proliferation, focus formation and anchorage-independent cell growth [78]. To explain the carcinogenicity of MCV, Feng et al. collected clinical MCC samples and found that the intergrated MCV genomes have mutations which result in prematurely turncated LT Ag or C-terminal truncations of MCV LT Ag [18]. The tumor-derived trunated MCV LT Ag (tLT) contains full open reading frame of ST Ag. They explained that removed of C-terminal region of MCV LT is necessary for MCV carcinogenicity [78].

SV40-transformed cells impair global genomic repair of CPD as mentioned previously [67]. MCV-positive cells also have poor GG-NER activity. In addition, MCV tLT Ag can inhibit GG-NER and XPC expression upon UV irradiation [79].

Protein functions of this new human cancer causing virus have not been well investigated. How the tLT Ag contribute to carcinogenesis? Whether it interacts with some caretakers to disrupt the genomic stability remains to be determined. The ST Ag of MCV also has predicted PP2A binding site [80]. Whether it plays roles on MCV carcinogenesis awaits for further investigation. It will be interesting to explore the common and novel features of the viral tumor Ag of MCV on DNA repair and genomic instability etc. The caretakers targeted by human polyomaviruses are summarized in Table 3.

6. Interaction between JCV/BKV viral Ags and DNA repair proteins

6.1. JCV LT Ag targets IRS-1

LT Ags of JCV and BKV bind and inactivate p53 and pRB as SV40 LT Ag does [21, 81]. In addition to direct interaction with p53 to disrupt DNA repair and genomic stability, JCV indirectly disrupts HRR. Khalili's group had a series of publications about the relationship of JCV and genomic instability. They found a novel mechanism for JCV LT Ag-mediated HRR repression. They examined clinical samples of progressive multifocal leukoencephalopathy and found that there are the Rad51 foci in inclusion bodies bearing oligodendrocytes. They used virus infected system to explore DDR and DNA repair upon viral infection. JCV-infected human astrocytes showed lower NHEJ activity. The γ-H2AX, Rad51 expression and micro-nuclei formation (marker of chromosome instability) increase in these cells. These indicated that induction of DDR and suppression of DNA repair did occur [82]. Additionally, they pinpointed that JCV LT Ag inhibits HRR indirectly. They initially noted that JCV LT Ag translocated insulin receptor substrate 1 (IRS-1) to nucleus [83]. IRS-1 is a cytosolic adaptor protein which involved in insulin receptor (IR) and insulin-like growth factor-1 receptor (IGF-1R) signaling. They found the IRS-1-Rad51 nuclear interaction in JCV LT Ag-positive medulloblastoma cells [84]. They demonstrated that JCV LT Ag translocated IRS-1 to nucleus and forced IRS-1-Rad51 complex formation. JCV LT Ag-positive medulloblastomas, defective in HRR recombinase Rad51 activity, therefore tended to mutation accumulation and sensitized to genotoxic agents. The presence of JCV LT Ag affects faithful HRR and DNA repair fidelity [85]. The DNA damages induced by LT Ag are repaired by error-prone NHEJ and have

threatened to genomic integrity. Given that JCV LT and IGF-1 pathway merge to destroy precise DNA repair and genomic integrity [86], LT Ag of JCV impairs HRR as does LT Ag SV40; however, it uses a novel mechanism to interfere HRR indirectly (Table 3) [86]. By using factor of IGF-1 pathway, JCV LT indirectly suppresses Rad51 activity and forces error-prone NHEJ. Besides, the nuclear IRS-1 was also detected in SV40 LT Ag expressing cells [87].

Virus	Viral proteins	Cellular targets	Impaired DNA repair	Refs
MCV	LT Ag	ATR	Induce DDR	78
	Tumor derived tLT Ag	XPC	GG-NER	79
JCV	LT Ag	p53	NER etc.	21,81
	ST Ag	PP2A	-	14,89,90
	Agnoprotein#	Ku70	NHEJ	16,88
	LT*	IRS-1 ^	Form nuclear IRS-1Rad51 complex, HRR	83-87
BKV	LT	p53	NER etc.	81

#: JCV agnoprotein bind to Ku70 and ST Ag through its N terminal.

*: JCV LT indirectly inhibit Rad51 via translocating IRS-1 to nuclear.

^: IRS-1 binds Rad51. It, via residue155-302, also binds LT Ags of JCV and SV40.

-: indicates not fully determined

Table 3. Cellular caretakers targeted by human polyomaviral antigens

6.2. JCV agnoprotein, ST Ag and DNA repair

Khalili et al. addressed the issue of low NHEJ activity in JCV-infected human astrocytes. Agnoprotein, a small product of late region (71 a.a.), of JCV was found to impair NHEJ. Agnoprotein reduces the expression of Ku70 and Ku80 NHEJ proteins. Agnoprotein, through its N terminal residues 18-36, directly binds to Ku70 and represses NHEJ activity [16, 88]. As we described on SV40 ST Ag, it interacts and inhibits PP2A. SV 40 ST Ag impairs NHEJ through PP2A binding. JCV ST Ag has been predicted and demonstrated to bind PP2A [14, 89, 90]. Our group found that JCV ST Ag, a PP2A inhibitor, also inhibits NHEJ. We suggest that the NHEJ inhibition activity of JCV-infected cells may be contributed by both agnoprotein and ST Ag. In our laboratory, we found that ST Ag of JCV impairs both NER and NHEJ activity. In JCV ST-expressing cells, the expression of XPD is lower than that in the vector-control cells [91].

The LT and ST Ags among SV40, JCV and BKV have high homology in protein sequence. For example, LT Ags of JCV, BKV and SV40 are above 70% homologous in protein sequence. In brief, LT Ags of JCV (688 a.a.), BKV (695 a.a.) and SV 40 (708 a.a.) bind p53, as well as ST Ag

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of those (below 70% homologous) that bind PP2A. However, they have different downstream effects on host due to host complexity. In permissive cells, they proceed to lytic life cycle, whereas in non-permissive cells, they transformed cells. Interaction of caretakers and SV40 LT Ag plays as a model for mechanism of transformation of other polyomaviruses in non-permissive host.

7. Interaction between MPyV viral Ag and DNA repair proteins

The study of MPyV, another well-studied animal polyomavirus, revealed a novel connection bewteen virus and DNA repair pathways. It represses DNA repair systems through its LT Ag by directly binding to a single-strand DNA binding protein, replication protein A (RPA), an essential DNA replication and repair protein [92]. For DNA repair, RPA plays as a sensor for UV-induced CPD to repair UV induced damage. When DNA encounters double-strand break, it also recuits MRN complex to damage lesions. MPyV LT Ag blocks RPA to DNA damage foci and leads to failure to recruit Rad51 etc. The OBD (origin binding domain, residue 262-420) of LT Ag mediated this inetraction. LT Ag or OBD induces DNA damage which is revealed by comet assay. In UV irradiated-MPyV LT Ag expressing cells, location of RPA is diffusely nuclear, rather than localization to damage foci. Rad51, the critical recombinase for HRR, is not recruited to foci. Rad 9, a component of sliding clamp complex for DNA repair, is also prevented to reach DNA damage foci by MPyV LT Ag.

Another study on MPyV also provides a link between DNA repair and virus replication. MPyV infcetion increases ATM activity and level of ATM^{S1981P}. It activates and utilizes a component(s) of an ATM pathway of DNA repair to prolong S phase and aids in its own replication [93].

Interestingly, SV40 LT antigen targets p53 directly, but MPyV LT does not [94]. However, MPyV ST and middle T antigens, as SV40 ST antigen, also form stable complexes with PP2A [69]. Differentially, these interactions eclict the activation of different cellular signal pathways involved in growth control [95]. There is no related publication about the effect of MPyV ST Ag and PP2A interaction on DNA repair. Nevertheless, the difference of PP2A binding subunits and PP2A substrates between ST Ags of SV40 and MPyV have pointed out the complexity and diversity of these groups of viruses [94].

8. Specific interaction between other viruses and DNA repair

Some other viruses also encode specific proteins to target DNA repair proteins as polyomaviruses do. The most famous DNA repair caretaker which is bound and/or degraded by viral proteins is tumor suppressor p53. In addition to SV40 LT Ag, E1B-55k/E4-ORF6 of adenovirus, E6 of human papillomavirus (HPV), vIRF1 of Kaposi's sarcoma-associated herpesvirus (KSHV) and X protein of hepatitis B viris (HBV) can bind and/or degrade p53 which plays the pivotal role in NER. Other viral proteins such as E1B-55k/E4-ORF6 and E4-ORF3 of adenovirus also interact and/or mislocalize MRN DNA repair complex as SV40 LT Ag. These interactions

repress NHEJ and HRR pathways. Interestingly, recent studies showed that herpes simplex virus-1 manupulates the Fanconi anemia pathway, redistributes FancD2, to inhibits NHEJ and promote viral replication cycle [96]. Several viral proteins target other DNA repair proteins which are not mentioned yet in polyomaviruses studies. X protein of HBV inhibits NER through interrupts DDB1 which recognizes UV damage site. E6 of HPV-8 inhibits XRCC1, a BER and single stranded breakage repair protein. Many viruses also activate or inactivate the ATM/ATR pathways to take the advantages for their life cycles. The interaction of viruses and host DNA repair machineries had been revealed in the past decade and were well reviewed in other articles [4, 5]. These viral proteins serve as useful tools for our understanding the function and important roles of these DNA caretakers.

9. Conclusions

The polyomaviruses are not closely associated with human cancers if compared with the other six Group 1 carcinogenic viruses (HPV, HBV, KSHV, human T-lymphotropic virus 1, hepatitis C virus and Epstein Barr virus). However, they transform cells of non-permissive host efficently and serve as an excellent model to investigate carcinogenesis. Some of polyomaviral antigens not only induce DNA damage but also block DNA repair pathways. They directly induce mutations and simutenously ruin the caretaker defense barriers. The viral proteins cooperate to accummulate mutations/chromosomal instability and initiate the birth of cancer. SV40 targets numerous caretakers to disrupt genomic intergrity and serves as a powerful model to gain insight of the complexity of DNA repair systems. It is worthwhile to note that there are novelties and differences among these viruses. Some LT Ags target p53, some do not. Human MCV is most closely related to human malignancy. The function of MCV LT Ag is dramatically different to that of SV40. The MCC tissues contain tLT and ST Ag. The lessons learned from SV40 will help to reveal the roles of MCV tLT and ST Ag on genomic instability. Especially, the homology among their ST Ags are lower than that of LT Ags. Bollag et al. claim that LT Ags have received much attention. JCV ST Ag binds PP2A and pRB and has only recently become a focus of study [91]. Additionally, SV ST Ag complements LT Ag, hTERT and Ras for the transformation of human mammary epithelial cells, but MPyV ST Ag does not. The differences between their ST Ags may depend on the differential utilization of PP2A. They bind different scaffold subunits of PP2A/A. The two ST Ags can target different proteins for dephosphorylation. As described in the Introduction section, virueses are always more complicated than our understanding. By studying the proteins and RNAs of cancer associated viruses, we can learn more lessons on DNA repair in further investigations.

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