### **Small DNA Tumour Viruses**

Edited by

Kevin Gaston

School of Biochemistry University of Bristol **Bristol** UK

#### caister.com/dna-tumour-viruses

Copyright © 2012

Caister Academic Press Norfolk, UK

www.caister.com

British Library Cataloguing-in-Publication Data A catalogue record for this book is available from the British Library

ISBN: 978-1-904455-99-8

Description or mention of instrumentation, software, or other products in this book does not imply endorsement by the author or publisher. The author and publisher do not assume responsibility for the validity of any products or procedures mentioned or described in this book or for the consequences of their use.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the publisher. No claim to original U.S. Government works.

Cover design adapted from Figure 1.3

Printed and bound in Great Britain

# Contents

	Contributors	V
	Preface	ix
1	Human Papillomavirus Infection and its Association with Neoplasia: From Molecular Biology to Prevention and Treatment Richard Oparka and C. Simon Herrington	1
2	The Art and Science of Obtaining Virion Stocks for Experimental Human Papillomavirus Infections  Michelle A. Ozbun and Michael P. Kivitz	19
3	The Regulation of Human Papillomavirus Gene Expression by the E2 Protein: Keeping a Finger in Every Pie Sheila V. Graham and Kevin Gaston	37
4	HPV E5: An Enigmatic Oncoprotein  Laura F. Wetherill, Rebecca Ross and Andrew Macdonald	55
5	E6 Oncoproteins: Structure and Associations Scott B. Vande Pol	71
6	Biochemical and Structure–Function Analyses of the HPV E7 Oncoprotein Leonardo G. Alonso, Lucía B. Chemes, María L. Cerutti, Karina I. Dantur and Gonzalo de Prat-Gay	99
7	Replication and Maintenance of Viral Genomes by Association with Host Chromatin  Koenraad Van Doorslaer, Vandana Sekhar, Jameela Khan and Alison A. McBride	125
8	Alterations in Cellular miRNAs Induced by Human Papillomaviruses Amy S. Gardiner, Abigail I. Wald and Saleem A. Khan	151
9	Viral Deregulation of DNA Damage Responses Sergei Boichuk and Ole Gjoerup	175
10	Structural 'Snap-shots' of the Initiation of SV40 Replication  Gretchen Meinke and Peter A. Bullock	195

#### iv | Contents

#### caister.com/dna-tumour-viruses

11	Human Papillomavirus DNA Replication: Insights into the Structure and Regulation of a Eukaryotic DNA Replisome Claudia M. D'Abramo, Amélie Fradet-Turcotte and Jacques Archambault	217
12	Induction of Genomic Instability by Human Papillomavirus Oncoproteins Karl Münger and Stefan Duensing	239
13	Targeting of Promyelocytic Leukaemia Proteins and Promyelocytic Leukaemia Nuclear Bodies by DNA Tumour Viruses Keith N. Leppard and Jordan Wright	255
14	Adenoviruses and Gene Therapy: The Role of the Immune System Laura White and G. Eric Blair	281
	Index	321

## Preface

The small DNA tumour viruses continue to provide new insights into many fundamental aspects of biology, including gene regulation, DNA replication, cell transformation, cell cycle control and tumorigenesis. The causal link between papillomaviruses and some human cancers is well known and has resulted in the development of effective vaccines that are coming into widespread use. A role for polyomavirus in human cancer has recently been established. Adenoviruses do not cause cancer in humans but, as well as providing excellent tools for the study of many host cell processes, these viruses have been exploited as delivery vehicles in gene therapy. A common feature of the small DNA tumour viruses is their heavy reliance on the host for survival

and replication. Understanding the virus-host relationship is critical to understanding the tumorigenic process and how these viruses subvert the host's immune system. The aim of this book is to provide an overview of the molecular biology of these viruses and some of their interactions with the host. Many of the chapters focus on human papillomavirus, reflecting the current volume of research in this area. However, in many cases comparisons are made with other viruses. Other chapters go beyond the papillomaviruses and focus on cellular pathways that are targeted by many viruses. I hope that this collection is a useful reference for those currently working in this field and a stimulating introduction for those new to this area.

Kevin Gaston



#### Α CDK see Cyclin-dependent kinase CDKI see Cyclin-dependent kinase inhibitor AAA+ (ATPases associated with various cellular Cell cycle 7-8, Fig. 1.4 activities) 206, 224 Centriole 188, 241-243, Fig. 12.2 Adenovirus 175, 184-187, 263-266, 281-286 Centrosome 10, 134, 188, 241-243, 261 E1A 102-103, Fig. 6.1, 285 Cervarix 13 E1B 265-266, 285-286, 294-296 Cervical cancer 1, 6, 12-13, 37, 55, 72, 84, 115-117, genome 282-283, Fig. 14.2 151, 153–156, 159–162 immune response 287, 293 Cervical glandular intraepithelial neoplasia (CGIN) 5-6 life cycle 283-285 Cervical intraepithelial neoplasia (CIN) 5-6, Fig. 1.3, 9, non-attenuated 296 12, 57, 117, 156 oncolytic 281-297, 301 Chaperone 60, Table 4.1, 114, 196 replication deficient 285-286 Chk2 230-231, 177-181, Fig. 9.1, Fig. 9.2, 188, 258, 260 structure 282, Fig. 14.1 ChlR1 43-44, 143-136, Table 7.1 vectors 285-287 Chromosomal instability see Genome instability serotypes 299 Claspin 177-178, 189, 248 ALT see Alternative lengthening of telomeres Cleavage and polyadenylation specificity factor Alternative lengthening of telomeres (ALT) 245, Fig. (CPSF) 41, 47 12.4, 261, 267 Cleavage stimulatory factor (CstF) 41 Amplification see HPV amplification C-myc 153, 246, 261, 263 Aneuploidy 184, 187-188, 239, 248 Complement 287, 292-293, 299 Angelman syndrome 83-84 Cottontail rabbit papillomavirus (CRPV) 21, 27–28, Angiogenesis 302 Apoptosis 10-12, 43, 63-64, 82, 88, 176, 179, 260-261, Coxsackie and adenovirus receptor (CAR) 283-284, 271-273, Fig. 13.3, 302 Fig. 14.3 activating factor (Apaf1) 10 CRPV see Cottontail rabbit papillomavirus Arenavirus 270 Cyclin-dependent kinase (CDK) 7–10, 113, 117–118, Ataxia-telangiectasia mutated (ATM) 175–176, 189, 241-245 177-188, Fig. 9.2, Fig. 9.3, 227, 230-231, 243 Cyclin-dependent kinase inhibitor (CDKI / CKI) 7–10, ATM and Rad3-related (ATR) 175-178, Fig. 9.1, Fig. 62 9.2, 230, 248, 258, 260 Cyclo-oxygenase-2 (Cox-2) 64 ATR see ATM and Rad3-related Cytokine 281, 288-294, Fig. 14.4, Fig. 14.5 Aurora kinase 140, 189, 248, 261 D В DAI see DNA-dependent activator of interferon BK virus (BKV) 211, Fig. 10.14, 267–268, 271, Fig. 13.3 Daxx 259, 261, 265-266, 269 Brd4 43, 87, 128, 133-138 Dendritic cells (DCs) 117 Bub1 136, Table 7.1, 182, Fig. 9.3 Dicer 152-153 C DNA damage 9-11, 89, 170, 175, 177-181, Fig. 9.1, CAR see Coxsackie and adenovirus receptor Fig. 9.2, 181–185, 188–189, 230–232, Fig. 11.5, Casein kinase 2 (casein kinase II/ CK2/ CKII) 9, 243-245, Fig. 12.4, 260 102-103, Fig. 6.1, 103, Fig. 6.2, 107-108, 113, 139 damage response (DDR) 175, 181, 188-189, Caspase 10-11, 189, 219, Fig. 11.1, 230, 260, 291-292, 229-231, 230 Fig. 14.5

melting 207–210, 205, 221–225, Fig. 11.3 replication 176, 195–198, 211–212, 217–233, 245 unwinding see DNA melting DNA-damage induced kinase (HIPK2) 258–260 DNA polymerase α-primase 183, 195, 225, DNA-dependent activator of interferon (DAI) 290–292 DNA-dependent protein kinase (DNA-PK) 176–177, Fig. 9.1, 179–185 DNA-PK see DNA-dependent protein kinase Double-strand DNA breaks (DSBs) 176–180, 186, 230 Drosha 152  E  E1 see HPV E1 protein E1^E4 see HPV E1^E4 protein E11 see Adenovirus E1A protein E18 see Adenovirus E1B protein E2 see HPV E2 protein E4 see HPV E5 protein E5 see HPV E6 protein E6 see HPV E6 protein E6 see HPV E7 protein E6 see HPV E7 protein E8*E2 see HPV E7 protein E8*E2 see HPV E8*E2 protein EBNA1 see Epstein-Barr nuclear antigen 1 eIF4E 259, 262 Epidermal growth factor (EGF) 59–62, 159 Epidermal growth factor receptor (EGFR) 56, Fig. 4.1, 59–62, Table 4.1, Fig 4.2, 159 Epidermodysplasia 3, Table 1.1, 55, 63 Epigenetic 249 Episome 4, 72, 128, 218 Epstein-Barr nuclear antigen 1 (EBNA1) 127, Fig. 7.1, 129–132, Fig. 7.4, 136–139, Fig. 7.5, 269, 270	HPV (human papillomavirus) amplification 5, 39, 58, 125, 188, 229–232 E1 protein 2, 38–39, Fig. 3.1, Table 3.1, 127, 142, 188, 217–232, Fig. 11.1, Fig. 11.3, Fig. 11.4 E1^E4 protein 2, 5, 11, 24–25, 39, Table 3.1, 40, Fig. 3.2, 45–46, 58 E2 protein 2, 11–12, 37–39, Fig. 3.1, Table 3.1, 40–47, Fig. 3.3, Fig. 3.4, Fig. 3.5, 113–114, 188, 217–225, Fig. 11.2 E2C protein 42, 114 E4 protein see E1^E4 E5 protein 55–65, Fig. 4.1, 72 E6 protein 8–9, 11–12, 40–42, 188–189, 240–247 and BAK 88 binding to E2 45 binding to E6AP 75–77 binding to PDZ proteins 79–80 binding to PDZ proteins 79–80 binding to PML 267 evolutionary origin 73–74 p53 binding 81–83 structure 71–90 E6* protein 80–81 E7 protein 9–12, 99–116, 188–189, 240–249 and PML 267 binding to E2 45, 113 binding to PDACs 112–113 binding to PDACs 112–113 binding to pocket proteins 101, Table 6.1, 108–110, 111–112 chaperone holdase activity 114 degradation 110 localisation 114–116 phosphorylation 107–108 soluble oligomers 114 structure 102–107 E8^E2 protein 39–44, 128, 141
Epstein–Barr virus (EBV) 126–143, 269, 271	genome 2–11, 19–27, 37–41, Fig. 3.1, 73, Fig. 5.2, 125–144
F Fanconi anaemia (FA) 178, 189, 243–245, Fig. 12.4 Fas-associated death domain (FADD) 10–11, 290	proteins 39, Table 3.1 high risk 2–3, 11–13, 58–64, 74–87, 111, 156, 239–249
<b>G</b> Gardasil 13 Genome instability 12, 152, 239–249, 180–184, 187–190	L1 protein 5, 13, 20, Table 2.1, 23–30, 48 LCR/URR (long control region/upstream regulatory region) 38, Fig. 3.1, 42–44, 218 low risk 2–3, Table 1.1, 11–12, 79–83, 87, 111–112, 151, 163 Human papillomavirus see HPV
HAT see Histone acetyltransferase	1
HAT see Histone acetyltransferase HDAC see Histone deacetylase Head and neck squamous cell carcinoma (HNSCC) 6, 38, 156, 189 Helicase 2, 38–39, Table 3.1, 127–128, 195–198, 203–210, 217–225, Fig. 11.1 Herpes simplex type 1 (HSV1) 126, 265, 268–272 Herpesviruses 126–141, 268 High-risk HPV see HPV Histone acetyltransferase (HAT) 86–87, 165, 249 Histone deacetylase (HDAC) 89, Fig. 5.6, 100–103, Table 6.1, 111–113, 165, 249	ICPO 183, 268–269 IFN see Interferon Immune modulation 299 Immunosuppression 293, 296 Integration 11, 41–45, Fig. 3.3, 73, Fig. 5.2, 114, 143, 231–232, 243, 249 Interferon (IFN) 113, 116, 226–127, 261–265, 268, 272–273, 281, 288–290, Fig. 14.4, Fig. 14.5 Integrin 4, 20, 44, 161, 284, Fig. 14.3, 298 Intrinsic disorder 105–106, Fig. 6.3

#### J

Jagged 88–89, Fig. 5.6 JC polyomavirus (JCV) 184, 211, Fig. 10.14, 267, 271 J-domain 196, 210

#### Κ

Kaposi's sarcoma-associated herpesvirus (KSHV) 126, 129–10, 132–133, 135–138, Table 7.1, 142 Koilocytes 5, Fig. 1.3, 62

#### L

L1 see HPV L1 protein
LANA 127, Fig.7.1, 129–133, Fig. 7.4, 135–140, Fig. 7.5, 142
Large T antigen see SV40 large T antigen
Lassa fever virus 270
LCR/URR see HPV LCR/URR
Low-risk HPV see HPV
LxCxE motif 73, 75, 88, 102–103, 109, Fig. 6.5, 111–114, 189
Lymphocytic choriomeningitis virus (LCMV) 270–271, Fig. 13.3

#### М

Macrophage depletion 294
MAGUK 9
Major histocompatibility complex (MHC) 56, 60–63, 262, 294
Matrix attachment region (MAR) 132, 262
MHC see major histocompatibility complex
miRNA (microRNA) 151–166
Mitotic accumulations of PML (MAPPs) 256
Mitotic spindle 101, Table 6.1, 134, 136, Table 7.1, 188, 241, 248
Mouse polyomavirus (MPyV) 183–184
Mre11-Rad50-Nbs1 (MRN) 175, 177–179, Fig. 9.2, 185–186, 265
MRN see Mre11-Rad50-Nbs1
mRNA stability 48

#### Ν

NHEJ see Non-homologous end-joining NOD-like receptors (NLRs) 287, 291–292, Fig. 14.5 Non-homologous end-joining (NHEJ) 179, 180, 186 Notch 88–90, Fig. 5.6 Nuclear matrix 46, 132, 142

#### 0

ONYX-015 286, 295, 296, 302 Organotypic 19–24, 29 Oropharyngeal squamous cell carcinoma (OPSCC) 156–157

#### P

p53 tumour suppressor protein (TP53) 7–9, 11–12, 44, 74–76, 78–79, 81–83, 86–87, 177–178, 182–184, 186, 189, 229, 240, 247, 295, and PML 260–261

PAMPS see Pathogen-associated molecular patterns Pap (Papanicolaou) smear 6,62,116

Papanicolaou see Pap smear Partitioning see Viral partitioning Pathogen-associated molecular patterns (PAMPs) 287, 292 Pattern recognition receptors (PRRs) 281, 287, 290–292 PDZ proteins see HPV E6 protein PML see Promyelocytic leukaemia protein PML nuclear bodies see Promyelocytic leukaemia protein PML oncogenic domains (PODS) see Promyelocytic leukaemia protein Polyomavirus 175, 181-183, 211-212, 267-268 Polyploidy 248-249 pRB see Retinoblastoma tumour suppressor protein Promyelocytic leukaemia protein (PML) 126, 247, 142, 183, 256, 263, 271, Fig. 13.3 isoforms 256, 257, Fig. 13.1 nuclear bodies **PODS** 

#### R

Retinoblastoma tumour suppressor protein (pRb) 9–10, 74–75, 100–105, 189, 241 degradation 108–110 E7 interaction 111–113 related proteins 10, 100–101, Table 6.1 RIG-1-like receptors (RLRs) 287, 290

#### S

Serine-arginine (SR)-rich proteins 47 -49
Single-strand DNA breaks (SSBs) 176, 230
Splicing 40, Fig. 3.2, 45, 47
Squamous cell carcinoma (SCC) 1, 6–7, 38, 156–157, 161–164
Squamous cell carcinoma of the head and neck (SCCHN) 156–158, Table 8.3, Fig. 8.2
SR proteins see Serine-arginine (SR)-rich proteins
SV40 large T antigen (T/T-Ag) 81, 102, 103, 114, 181, 184, 195–212
helicase 195–212
OBD (origin binding domain) 196-212
spiral hexamer 201–203

#### Т

T antigen see SV40 large T antigen
Telomerase reverse transcriptase (hTERT) 9, 246, 261
TERT see Telomerase reverse transcriptase
Toll-like receptors (TLRs) 287
TopBP1 43, 134–135, 177, 186
Topoisomerase 224 195, 224

#### U

Ubc9 226, 228, 232, 265 Ubiquitination 82–84, 108, 110, 228, 258 URR see HPV long control region

#### ۷

Vaccine 12–13, 116–117, 143, 286, 299–300 Vacuolar ATPase 60–61 Varicella zoster virus (VZV) 126, 269–273 Viral partitioning 127–141, Fig. 7.2

#### caister.com/dna-tumour-viruses

Viroporin 57,65 Virus-like particle (VLP) 13,20,28–30 VRX-007 295–296 Vulvar intraepithelial neoplasia (VIN) 5

W

Warts 11-2, 19-22, Table 2.2, 29, 37

Χ

Xenograft 20, 22, 28, 295, 301, 302