Advances in Experimental Medicine and Biology 879

Janos Minarovits
Hans Helmut Niller *Editors*

Patho-Epigenetics of Infectious Disease

Springer

Advances in Experimental Medicine and Biology

Volume 879

More information about this series at http://www.springer.com/series/5584

Janos Minarovits • Hans Helmut Niller
Editors

Patho-Epigenetics of Infectious Disease

Springer

Editors
Janos Minarovits
University of Szeged
Szeged, Hungary

Hans Helmut Niller
University of Regensburg
Regensburg, Germany

ISSN 0065-2598 ISSN 2214-8019 (electronic)
Advances in Experimental Medicine and Biology
ISBN 978-3-319-24736-6 ISBN 978-3-319-24738-0 (eBook)
DOI 10.1007/978-3-319-24738-0

Library of Congress Control Number: 2015957434

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Foreword

During recent years, the study of epigenetic phenomena in genetics has attracted increasing interest in all fields of biology and medicine. In epigenetics, we are dealing with a gamut of regulatory mechanisms based on the methylation of DNA, multiple histone modifications, the activity of small RNA's, and additional, so far, incompletely understood biochemical reactions. While there is solid evidence to support the role of these functions as participants in the regulation of genetic activities, it remains to be elucidated which modulations epigenetic regulators are subject to. Today, epigenetic mechanisms are held at least partly responsible for the causation of:

- Complex human diseases (from tumor to psychiatric) with evident or surmised genetic background
- Genetic imprinting and its defects important in the clinic
- Environmental effects on the genome
- Modulations in the course of infectious diseases
- Hitherto poorly investigated phenomena in developmental biology or decisive events during evolution
- Genome-wide sequelae of genome manipulations, e.g., by the insertion of foreign DNA

The similarity of DNA sequences, e.g., between chimpanzees and humans (about 95 %), and the obvious differences between these organisms have raised numerous tantalizing questions about the importance of regulatory mechanisms during evolution and the evolving phenotypes of different species.

The patho-epigenetics of infectious diseases is an important case in point. For decades, students of *Mycobacterium tuberculosis*, to name just one example, had to cope with the vagaries of this disease, its variability in pathology and enigmatic susceptibility of humans exposed to it, as well as the unpredictable response of patients to this infection and its treatment. In this context, epigenetics immediately comes to mind and is now being investigated in a number of laboratories.

In the volume *Patho-Epigenetics of Infectious Diseases* edited by Janos Minarovits (Szeged) and Hans Helmut Niller (Regensburg), major aspects of the role of epigenetic mechanisms have been addressed in a series of model infections, both viral – human immunodeficiency virus and Epstein-Barr virus – and bacterial. To set the stage for the informed reader, basic mechanisms have been discussed in an introductory chapter on *Epigenetic*

Regulation authored by the editors and their colleagues. In the following sections which are dealing with specific pathogens, the emphasis has been placed on the epigenetic consequences of infections in the host genomes.

Both, specialist in infectious diseases and the newcomer with an interest in epigenetics, will be attracted to this volume which has been edited by experts in the field. For many years, the authors of individual chapters have made important contributions to epigenetic aspects of the infectious diseases which they had specialized in. This book will become a valuable addition to many researchers' library.

walter.doerfler@viro.med.uni-erlangen.de Walter Doerfler
Institute of Clinical and Molecular Virology
University Hospital Erlangen-Nürnberg
D-91054, Erlangen, Germany

Institute of Genetics
University of Cologne
Köln, Germany

Preface

Epigenetic regulatory mechanisms ensure the heritable alterations of cellular states without affecting the nucleotide sequence of the DNA. In multicellular organisms belonging to the taxon *Eukarya* or *Eukaryota*, epigenetic control of transcription forms the basis for the phenotypic and functional diversity of various cell types that carry identical or nearly identical genomes. Epigenetic regulators affect chromatin structure and promoter activity by depositing stable, but reversible, marks on DNA or DNA-associated proteins. Such epigenetic marks ensure the faithful transmission of gene expression patterns to each progeny cell upon division (*epigenetic memory*).

The diverse epigenetic regulators act in concert to establish cell type-specific gene expression patterns in multicellular organisms. Disturbances in epigenetic control mechanisms, elicited by a variety of agents, may result, however, in pathological changes and disease development, as overviewed earlier (*Patho-Epigenetics of Disease. Eds*. Minarovits J. and Niller H.H. Springer Science and Business Media, New York, 2012). One of the pioneering observations connected viral DNA integration with epigenetic alterations and tumorigenesis in model organisms (reviewed by Doerfler 2012). This volume focuses on epigenetic dysregulation and patho-epigenetic processes caused by microorganisms, mainly viruses and bacteria infecting humans.

In the first chapter *Janos Minarovits*, *Ferenc Banati*, *Kalman Szenthe*, *and Hans Helmut Niller* briefly outline the major, "classical" epigenetic regulatory mechanisms that include DNA methylation, modifications of core histone proteins, as well as polycomb group (PcG) and trithorax group (TrxG) protein complexes that may also modify histones or affect chromatin compaction directly. This chapter also deals with novel epigenetic regulators such as variant histones, pioneer transcription factors, long noncoding RNA molecules, and proteins controlling long-distance chromatin interactions; it also gives a brief characterization of various chromatin types.

In Chap. 2, *Enass A. Abdel-Hameed*, *Hong Ji*, *and Mohamed Tarek Shata* summarize how the HIV provirus, i.e., the DNA copy of the human immunodeficiency virus (HIV) genome, undergoes epigenetic modifications in host cells and how the viral proteins affect the cellular epigenome and gene expression pattern. They also discuss the potential use of epigenetic drugs, in combination with highly active antiretroviral therapy (HAART), to eradicate latent HIV genomes from the cells of HIV-infected and AIDS patients.

In Chap. 3, *Hans Helmut Niller*, *Ferenc Banati*, *Daniel Salamon*, *and Janos Minarovits* describe the host cell-dependent epigenotypes of Epstein-Barr virus (EBV), the first human tumor virus which is associated with a series of malignant human tumors. EBV, a gammaherpesvirus, infects both lymphoid and epithelial cells, and epigenetic dysregulation caused by the latent, growth transformation-associated viral oncoproteins plays a role in the initiation and progression of EBV-associated neoplasms.

Epigenetic reprogramming of host cells by oncoviruses appears to be a general phenomenon. In Chap. 4, *Janos Minarovits*, *Anett Demcsák*, *Ferenc Banati*, *and Hans Helmut Niller* overview the complex epigenetic changes caused by human tumor viruses or tumor-associated viruses including Kaposi's sarcoma-associated herpesvirus (KSHV), hepatitis B virus (HBV), hepatitis D virus (HDV), hepatitis C virus (HCV), human papillomavirus (HPV), Merkel cell polyomavirus (MCPyV), and human T-cell lymphotropic virus type I (HTLV-I).

Recently, there were significant efforts to elucidate the epigenetic alterations caused by bacterial pathogens in infected cells and organisms. In Chap. 5, *Lorenzo Chiariotti*, *Lorena Coretti*, *Raffaela Pero*, *and Francesca Lembo* evaluate the data demonstrating that lipopolysaccharide (LPS), the major component of the outer membrane of most Gram-negative bacteria, elicits not only inflammatory reaction but also short-term and long-term epigenetic changes in innate immune cells and epithelial cells. The latter phenomenon, i.e., LPS-mediated epigenetic reprogramming of human monocytes, monocyte-derived macrophages, dendritic cells (DCs), and neutrophils, may result in LPS- or endotoxin tolerance (ET). ET is characterized by the incapacity to produce proinflammatory cytokines and by other dysfunctions that may influence the host response to further encounters with microorganisms.

In addition to LPS, other bacterial products including various toxins, surface proteins, and effector proteins produced by obligate or facultative intracellular bacteria also elicit epigenetic alterations in their target cells. In Chap. 6, *Hans Helmut Niller and Janos Minarovits* describe how these bacterial products elicit histone modifications, i.e., alter the "histone code." Certain bacterial pathogens induce alterations of host cell DNA methylation patterns, too. Such changes in the host cell epigenotype and gene expression pattern may hinder the antibacterial immune response and create favorable conditions for bacterial colonization, growth, or spread. In addition, chronic inflammation caused by bacterial pathogens may also affect the epigenotype of host cells indirectly, via the enhanced production of inflammatory mediators.

Szeged, Hungary — Janos Minarovits
Regensburg, Germany — Hans Helmut Niller

Reference

Doerfler W (2012) The impact of foreign DNA integration in tumor biology and evolution via epigenetic alteration. In: Minarovits J, Niller HH (Eds) Patho-epigenetics of disease. Springer Science and Business Media, New York, pp 1–14

Contents

Abbreviations

5-azadC	5-Aza deoxycytidine
5caC	5-Carboxyl cytosine
5fC	5-Formyl cytosine
5hmC	5-Hydroxymethyl cytosine
5mC	5-Methyl cytosine
ACH	Active chromatin hub
AIDS	Acquired immunodeficiency syndrome
ATL	Adult T-cell leukemia/lymphoma
BAHD1	Bromo-adjacent homology domain-containing protein 1
BALF5	BamHI-fragment A leftward frame 5
BARF	BamHI-fragment A rightward frame
BART (=CST)	BamHI-fragment A rightward transcripts
BCBL (=PEL)	Body cavity-based lymphoma
BHRF1	BamHI-fragment H rightward frame 1
BL	Burkitt lymphoma
BMDC	Bone marrow-derived stem cell
BRLF1	BamHI-fragment R leftward frame 1
BZLF1	BamHI-fragment Z leftward frame 1
CagA	Cytotoxicity-associated antigen
CBP	CREB-binding protein
ccc	Covalently closed circular
CCR5	C-C chemokine receptor type 5
CGI	CpG island
CHD1	Chromodomain helicase DNA-binding protein 1
CIMP	CpG island methylator phenotype
CIN	Cervical intraepithelial neoplasia
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
COX-2	Cyclooxygenase-2
Cp	C promoter
CpG	A 5′-cytosine-phosphate-guanine-3′ dinucleotide
CST (=BART)	Complementary strand transcripts
CTCF	CCCTC-binding factor
DC	Dendritic cell
DLBCL	Diffuse large B-cell lymphoma
DMR	Differentially methylated region
DNMT	DNA methyltransferase

DNMTI	DNMT inhibitor
DUB	Deubiquitinase
E6, E7	HPV early region proteins 6, 7
EBER	Epstein-Barr-encoded small RNAs
EBNA	Epstein-Barr nuclear antigen
EBNA-LP	EBNA-leader protein
EBV	Epstein-Barr virus
EBVaGC	EBV-associated gastric carcinoma
EC	Elite controller
EMT	Epithelial mesenchymal transition
ET	Endotoxin tolerance
EZH1	Enhancer of zeste homolog 1 (PRC2 component)
EZH2	Enhancer of zeste homolog 2 (a HKMT, PRC2 component)
FoxA	Forkhead box protein A (a pioneer transcription factor)
GC	Germinal center
H1	Histone 1
H2A	Histone 2A
H2A.X	Histone 2A, variant family member X
H2A.Z	Histone 2A, variant family member Z
H2AK119ub1	Histone 2A mono-ubiquitinated at lysine 119
H2B	Histone 2B
H3	Histone 3
H3K27ac	Histone 3 acetylated at lysine 27
H3K27me3	Histone 3 tri-methylated at lysine 27
H3K4me3	Histone 3 tri-methylated at lysine 4
H3S10ph	Histone 3 phosphorylated at serine 10
H4	Histone 4
HAART	Highly active antiretroviral therapy
HAT	Histone acetyl transferase
HBV	Hepatitis B virus
HBx	HBV X-gene/protein
HBZ	HTLV-I basic leucine zipper factor
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDAC	Histone deacetylase
HDACI	HDAC inhibitor
HDV	Hepatitis delta virus
HHV	Human herpes virus
HIV	Human immunodeficiency virus
HKMT	Histone lysine methyl transferase
HL	Hodgkin lymphoma
HLA	Human leukocyte antigen
HMG	High mobility group protein
HMT	Histone methyl transferase
HNSCC	Head and neck squamous carcinoma
HOX	Homeobox
HP1a	Heterochromatin protein 1a

HPV	Human papilloma virus
HSV	Herpes simplex virus
hTERT	Human telomerase reverse transcriptase
HTLV	Human T-cell lymphotropic virus
HUS	Hemolytic uremic syndrome
HVS	Herpesvirus saimiri
IE	Immediate early
IEC	Intestinal epithelial cells
IFN-γ	Interferon gamma
Ig	Immunoglobulin
IL	Interleukin
InlB	(Listeria) Internalin B
ISGs	Interferon-stimulated genes
IκB	Inhibitor of NF-κB
JMJD	Jumonji domain
Kcr	Crotonylated lysine
kDA	Kilodalton
KDM	(Histone) Lysine demethylase
KS	Kaposi sarcoma
KSHV (=HHV-8)	Kaposi sarcoma herpes virus
L1-TRp	Terminal repeat promoter for LMP1
LAD	Lamina-associated domain
LANA	Latency-associated nuclear antigen
LC	Lymphoblastoid cell
LCL	Lymphoblastoid cell line
LCR	Locus control region
LCV	Legionella-containing vacuole
LECA	Last eukaryotic common ancestor
lincRNA	Long intergenic noncoding RNA
LINE	Long interspersed nuclear element
LLO	Listeriolysin O
LMP	Latent membrane protein
LMP1p	LMP1 promoter
LMP2Ap	LMP2A promoter
lncRNA	Long noncoding RNA
LntA	Listeria nuclear targeted protein A
LOCK	Large organized chromatin lysine (K9) modified regions
LPS	Lipopolysaccharide
LSD1	Lysine-specific histone demethylase 1
LTNP	Long-term nonprogressor
LTR	Long terminal repeat
MAR	(Nuclear) Matrix attachment region
MBD	Methyl-CpG-binding domain
MBP	Methyl-binding protein
MCD	Multicentric Castleman's disease
MCPyV	Merkel cell polyoma virus

MeCP2	Methyl-CpG-binding protein 2
MeDIP-chip	Methylated DNA immune precipitation-microarray hybridization
MeDIP-seq	Methylated DNA immune precipitation-sequencing
MHC	Major histocompatibility complex
miR-155	Micro RNA-155
miRNA	Micro RNA
MTase	Methyl transferase
NaBT	Sodium butyrate
ND10	Nuclear domain 10
NF-κB	Nuclear factor kappa B
NK cells	Natural killer cells
NPC	Nasopharyngeal carcinoma
NUE	(Chlamydia) Nuclear effector
OAMZL	Ocular adnexal marginal zone B-cell lymphoma
OGT	O-linked N-acetylglucosamine [GlcNAc] transferase (a PRC1 component)
PARP	Poly-ADP-ribose polymerase
PBMC	Peripheral blood mononuclear cell
PC	Polycomb (a PRC1 component)
PcG	Polycomb group
PCNA	Proliferating cell nuclear antigen
PD	Periodontal disease
PEL (=BCBL)	Primary effusion lymphoma
PKR	Protein kinase R
PML-NBs	Promyelocytic leukemia-nuclear bodies
PPIase	Peptidyl prolyl cis-, trans-isomerase
PRC	Polycomb repressive complex
PRMT	Protein arginine *N*-methyltransferase
PSI	Post-septic immunosuppression
PTLD	Posttransplant lymphoproliferative disease
Qp	Q promoter
ROS	Reactive oxygen species
SAM	S-adenosyl-L-methionine
SENP	Sentrin-specific protease
SET	Suppressor of variegation 3-9 [Su(var)3-9], enhancer of zeste and trithorax (a HKMT prototype)
SUMO	Small ubiquitin-like modifier
SUZ12	Suppressor of zeste 12
TAD	Topologically associated domain
Tax	Transactivator from the HTLV-I X-gene region
TCGA	The Cancer Genome Atlas Research Network
TET	Ten-eleven translocation
TGF-β	Transforming growth factor beta
Th cell	T helper cell
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor alpha