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Tapas K. Kundu  
Editor

# Epigenetics: Development and Disease

 Springer

*Editor*

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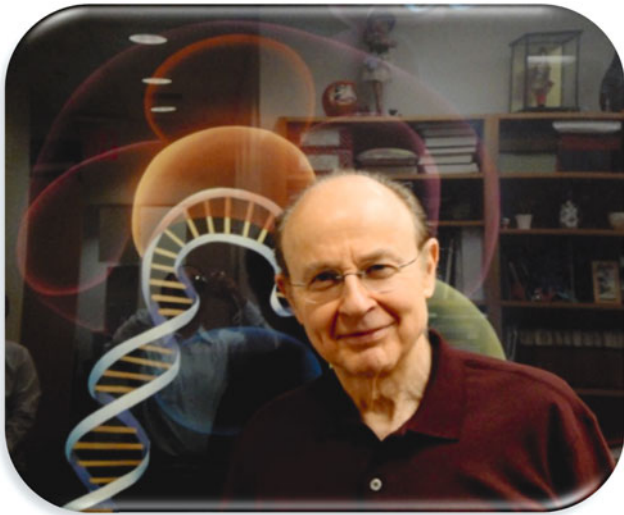
To

*A teacher, a mentor and a source of constant  
inspiration, **Prof. G. Padmanaban**,  
distinguished biotechnologist and  
former Director of Indian Institute  
of Science, Bangalore-12, India.*





# Foreword



“Our interest in and understanding of the concept of epigenetics has increased dramatically in the past decade, with the general perception of epigenetics having evolved from one of a phenomenon considered to originate from anomalous and disparate patterns of inheritance to one that is linked to a variety of normal and disease-related physiological processes through specific molecular mechanisms. Notably in this regard, the field of epigenetics has come a long way from an early predominant emphasis on DNA methylation to the current inclusion of chromosomal histone modifications and, more recently, non-coding RNAs in epigenetic regulatory events.

Epigenetic phenomena are intimately related to chromatin structure and organization and thereby influence gene expression. The importance of epigenetics for development and cell differentiation is increasingly clear and underlying mechanisms

are being unraveled. Similarly, epigenetic changes are now being linked to early events in the pathogenesis of diseases such as cancer, diabetes, and many others. These revelations have sparked efforts to develop new generation therapeutics against components of the epigenetic machinery for the treatment of complex multifactorial diseases.

This collection entitled *Epigenetics: Development and Disease* very effectively covers the above-mentioned aspects of epigenetics research, along with considerations of the evolution of the epigenetic machinery and the role of epigenetics in transcriptional regulation, in five separate parts. The various chapters in these parts have been written by experts who themselves have contributed significantly to their respective fields. Although there are other books with similar titles, this book provides a comprehensive update on the role of epigenetics in development and disease, efforts to develop therapeutics for some of these diseases and the role of epigenetics in transcriptional regulation. Consideration of the latter topic is especially important in view of the probable key role of transcription factors in the initial induction or establishment of many epigenetic changes or states – as dramatically evidenced by the ability of small subsets of ectopic transcription factors to reprogram somatic cells to pluripotent states through epigenetic changes.

Last but not least, the editor, Tapas K. Kundu, himself is an active scientist in the field and deserves a great deal of appreciation for his excellent job in conceiving and bringing to fruition this book. Students, as well as established investigators, will find the book to be a stimulating overview of the field.’

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and Molecular Biology  
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Robert G. Roeder, Ph.D.  
Arnold and Mabel Beckman Professor

# Preface

The field of ‘Epigenetics’ has moved on from the Waddington concept proposed in the year 1942; the definition has undergone a constant expansion and the scope of this subject has broadened over the years. The actual resurrection of the field can be marked by the discovery of the first histone acetyltransferase, GCN5, in the year 1995 by David Allis’ group. Although the activity of histone modifications (acetylation and methylation) and its role in the transcriptional activation was discovered by Vincent Allfrey in 1964 in a very elegant manner, its significance could only be appreciated by the scientific community after the identification of the GCN5 acetyltransferase and the subsequent expansion of the histone modifying enzymes family. Initially epigenetics and DNA methylation mediated gene regulation was thought to be synonymous. However, this concept has now been replaced with the understanding that these modifications along with DNA methylation form the basis of epigenetic phenomenon. However, all the histone modifications need not be involved at the same time in this event. Furthermore, it has also been realised that several non-histone proteins which can harbor the similar modifications such as acetylation and methylation also form an integral component of the epigenetic network.

I was fortunate to be associated with the growth of the field since 1996 during my days in the Roeder (Robert G Roeder) Laboratory in the Rockefeller University, where a majority of my work was towards understanding the mechanism of transcriptional regulation by histone acetyltransferase complexes and their recruitment in the activator dependent transcription from chromatin. Coincidentally, at the same time I was also a part of the discovery of the first p300 and PCAF acetyltransferase activity specific inhibitors (a collaboration with Philip Cole’s group). It is during this time that I got the opportunity to interact with Vincent Allfrey, David Allis and Jerry Workman. Interaction with Vincent Allfrey was really memorable. Vincent’s approach towards the discovery of histone modifications was really a bold step in the late 1960s when the use of radioactive material was difficult even at the Rockefeller University. However, Vincent was confident and optimistic about the histone modification field and its link to epigenetics. When I met him for the last time, it was coincident with Elizabeth Pennisi’s article in *Science*, highlighting the discovery of acetylation; the last line of which read “Vincent Allfrey should be pleased”.

I found that indeed Vincent was really happy. Vincent passed away soon in the year 2002.

Back home in India, I continued in the field, focussing on the regulation of chromatin dynamics by non-histone chromatin proteins, histone chaperones and also small molecule modulators of histone modifying enzymes. At this juncture, in 2007, I got an opportunity to edit a volume of *Subcellular Biochemistry* entitled 'Chromatin and Disease' (Vol. No. 41). While editing this volume I started realizing that chromatin function is tightly linked to epigenetic phenomenon and that the next volume must be on 'Epigenetics'. I thank the editorial board members, especially, Robin Harris and Dipak Dasgupta, who were so forthcoming and encouraging that I took the responsibility to edit the present volume entitled 'Epigenetics: Development and Disease'.

Epigenetics is not the monopoly of eukaryotes. During the course of evolution, as the genomic organization became more complex and evolved into systematically arranged chromatin structure, epigenetic machineries also started appearing as early as in Archaea. It is interesting to learn that soon after protozoans, all the four core histones along with different variants, ATP dependent remodeling systems and histone modifying enzymes are involved in genome function and thereby in the process of differentiation. In higher eukaryotes, epigenetically regulated dynamic chromatin function is the fundamental basis of differentiation and development. One of the basic cellular processes through which the epigenetic machineries operate is transcriptional regulation. Besides RNA Polymerase II driven transcription, RNA Polymerase I and RNA Polymerase III mediated transcription also requires histone modifications and promoter methylation. The non-coding RNA transcripts transcribed by RNA Polymerase III themselves function as one of the components of epigenetic machineries.

Cellular homeostasis is often disturbed in pathophysiological conditions. Thus in different diseases, inflammatory to infectious, epigenetic marks are altered during the disease progression. The consequent alteration of gene expression network is also remarkable. However, it is not yet established whether altered epigenetic marks are a cause or result of the diseased microenvironment. Nevertheless, the altered epigenetic marks are emerging as targets of new generation therapeutics, some of which are already in the advanced stages of drug development. Considering these facts, the present volume has been organized into five different parts: (i) Epigenetics and Evolution, (ii) Developmental Epigenetics, (iii) Epigenetics and transcription regulation, (iv) Epigenetics and Disease and (v) Understanding of Epigenetics: A Chemical Biology Approach and Epigenetic Therapy.

Experts from all over the globe (14 countries) have contributed excellent articles covering the thoughts expressed above. They have modified their article based on the reviewers' and my comments as and when they were requested, in spite of their heavily loaded schedule. I express my heartfelt thanks to all the contributors for their great effort. Several of my present laboratory colleagues and a few who have left the laboratory and gone abroad to pursue their further research career have contributed immensely to make this volume a reality, among whom I must acknowledge B Ruthrotha Selvi (presently at MRC HGU, Edinburgh, UK) and my present

lab colleagues Sujata Kumari and D. Karthigeyan. I also acknowledge Parijat Senapati and Snehajyoti Chatterjee without whose constant effort for more than a year, in the process of sending out invitation letters, time to time communications, organising the articles and giving several scientific inputs, publishing this volume would have been impossible. I, my research team as well as all the contributors greatly acknowledge all the reviewers who have worked so hard from behind the scenes for their valuable comments to improve each article.

This book is dedicated to Prof. G. Padmanaban, who is not only associated in all the scientific ventures I am involved in but has also played an active role in maturing the idea of the whole book through several discussions. I am at a loss of words to express my gratitude towards him. Last but not the least, I thank the past and present staff members of Springer, Max Haring, and Marlies Vlot, who worked hard with us to bring this volume for all of you. All the contributors and myself hope that this volume will be useful to students who are learning chromatin biology and epigenetics, the teachers and researchers of the field, and also scientists from pharmaceutical industries.

Bangalore-64

Tapas K. Kundu



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# Abbreviations

5-Aza-CdR	5-aza-2'-deoxycytidine
5hmc	5-hydroxymethylcytosine
5mC	5-methylcytosine
7SKsnRNP	7SK small nuclear ribonuclear protein
AAP	ambient air pollution
ABC	ATP-binding cassette
AML	acute myeloid leukaemia
APC	antigen-presenting cell
APOBEC3G	Apolipoprotein B mRNA-editing enzyme-catalytic polypeptide-like protein 3G
APP	Amyloid beta (A $\beta$ ) precursor protein
AR	Androgen receptor
ARE	Antioxidant response element
ART	Anti-retroviral therapy
ASC	adult stem cells
ATF2	Activating transcription factor 2
ATM	Ataxia telangiectasia mutated
ATR	Ataxia telangiectasia related gene
ATRX	Alpha thalassemia/mental retardation syndrome X-linked
BBB-	Blood brain barrier
BRCA1	Breast cancer 1, early onset
BRG1	Brahma-related gene 1
CAF-1	Chromatin assembly factor-1
CAP	catabolite activator protein
CARM1	Coactivator-associated arginine methyltransferase 1
CAST	CD3 epsilon-associated signal transducer
CBF-1	C-promoter Binding Factor-1
CCL19	C-C motif chemokine 19
CCL21	C-C motif chemokine 21
CcrM	cell cycle regulated methyltransferase
CD	chron's disease

Cdk9	Cyclin-Dependent Kinase 9
CDKN2	Cyclin dependent kinase 2
CENP-A	Centromere protein A
CF	core factor
CHD7	Chromodomain helicase DNA-binding protein 7
ChIP	Chromatin immunoprecipitation
CNS	conserved non-coding sequence
CNS	central nervous system
CpG	cytosine-phosphate-guanine
CREB	c-AMP response element binding protein
CRFs	Chromatin reassembly factors
CSB	Cockayne syndrome B protein
CSC-	Cancer stem cell
CSP-	Carbon nanospheres
CTCF	CCCTC-binding factor
CTD	Carboxy-Terminal Domain
CTIP2	Chicken ovalbumin upstream promoter transcription factor interacting proteins 2
CTK7A-	Sodium 4-(3,5-bis(4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)benzoate
CTL	Cytotoxic T-Lymphocytes
CTPB-	N-(4-Chloro-3-trifluoromethyl-phenyl)-2-ethoxy-6-pentadecyl-benzamide
DAC	5-deoxy-azacytidine
Dam	DNA adenine methyltransferase
DAPK1	Death associated protein kinase 1
Dcm	DNA cytosine methyltransferase
DEP	diesel exhaust particles
DNMT	DNA methyltransferase
DNMT1/3A/3B/3L	DNA methyltransferase 1/3A/3B/3L
DR3	death receptor 3
DSB-	Double strand break
EGCG	(-)-Epigallocatechin gallate
EMT	epithelial-to-mesenchymal transitions
eNoSC	energy-dependent nucleolar silencing complex
EPC	epithelial progenitor cells
ER	Estrogen receptor
ESC	embryonic stem cells
ESCC-	Esophageal squamous cell carcinoma
ETS	external transcribed spacer
FACT	facilitates chromatin transcription
FGF	fibroblast growth factor
GADD45 $\alpha$	growth arrest and DNA damage inducible protein 45 alpha
GFP	Green Fluorescent Protein
GMCSF	Granulocyte macrophage colony stimulating factor

H2AK119u	ubiquitinated histone H2A at lysine 119
ubiquitinated	histone H2A at lysine 119
H3K27me3	trimethylated lysine 27 on histone H3
H3K4me1/2/3	mono-di-tri-methylated histone H3 at lysine 4
H3K64me3	trimethylated histone 3 at lysine 64
H3K9ac	acetylated histone H3 at lysine 9
H3K9me1/2/3	mono-di-tri-methylated histone H3 at lysine 9
H4K20me3	trimethylated histone 4 at lysine 20
HAT	histone acetyltransferases
HATi	histone acetyltransferases inhibitor
HCC-	Hepatocellular carcinoma
HDAC	Histone deacetylase
HDACi	histone deacetylase inhibitor
HDMs	histone demethylases
HEXIM1	HMBA Inducible protein 1
HEXIM2	HMBA Inducible protein 2
HIV-	Human immune deficiency virus
HMBA	Hexa Methylene Bis Acetamide
HMG	high mobility group
HMTs	histone methyltransferases
HP1 $\alpha$	Heterochromatin protein-1 $\alpha$
HPC	high CpG promoter
HS	hypersensitive sites
HSC	hematopoietic stem cells
IBD	inflammatory bowel disease
ICM	inner cell mass
IG	isogarcinol
IGS	intergenic spacer
IKK	I $\kappa$ B kinase
IL	interleukin
INO80	Inositol-requiring protein 80
iPSC	induced pluripotent stem cells
ISWI	Imitation SWI
ITS	internal transcribed spacer
JMJD3	jumonji-domain-containing protein histone deacetylase 3
KAT-	Lysine (K) acetyltransferase
KDAC-	Lysine deacetylase
LARP7	La related protein
LAT	Latency associated transcripts
lncRNAs	long non coding RNAs
LPC	low CpG promoter
LSF	Late SV40 Factor
MBD	methyl-binding domain
MBD2	Methyl-CpG-binding domain protein 2
MBD3	methyl-CpG binding domain protein 3

MBP	myelin basic protein
MDMs	Monocytes derived macrophages
MEPCE	Methyl phosphate capping enzyme
MHC	major histocompatibility complex
miRNAs	microRNAs
MLL	Histone methyl transferase
MOZ-	Monocytic leukaemia zinc-finger protein
mRNAs	messenger RNAs
MS	multiple sclerosis
MZ	monozygotic
ncRNAs	non coding RNAs
NER	nucleotide-excision repair
NF- $\kappa$ B	Nuclear factor- $\kappa$ B
NFAT	nuclear factor of activated T cell
NK	natural killer
NOD	non obese diabetic
NoRC	nucleolar remodelling complex
NORs	nucleolar organiser regions
NPM-	Nucleophosmin
NSC	neural stem cells and progenitors
ORC-	Origin recognition complex
p300/CBP	E1A binding protein p300/CREB-binding protein
Paf1c	Polymerase-associated factor 1 complex
PAF53	RNA Polymerase I associated factor 53
PARP-1	poly-ADP-ribose-polymerase 1
PBMC	peripheral blood mononuclear cell
PCAF	p300/CBP-Associated Factor
PcG	polycomb group of proteins
PEPCK-	Phosphoenolpyruvate carboxykinase
PGC	primordial germ cells
PGC-1 $\alpha$	peroxisome proliferator activated receptor gamma coactivator 1
PIC	pre-initiation complex
PMA	Phorbol 12-Myristate 13-Acetate
Pol	RNA polymerase
PRC2	Polycomb repressive complex 2
PRMT	Protein arginine methyl transferases
PRMT6	Protein arginine methyl transferase 6
pRNA	promoter RNA
pTEFb	Positive Transcription Elongation Factor b
PTM-	Post translational modification
PTRF	Pol I and transcript release factor
r	ribosomal
RA	rheumatic arthritis
RbBp5	retinoblastoma-binding protein 5
RDR2	RNA-dependent RNA polymerase 2



RFX1	regulatory factor X 1
RISC	RNA induced silencing complex
R–M	restriction – modification
RNS	Reactive nitrogen species
ROR $\gamma$ t	RAR-related orphan receptor $\gamma$
ROS	Reactive oxygen species
RSS	RNA silencing suppressor
SAHA-	Suberoylanilide hydroxamic acid
SAM	S-adenosyl methionine
SCF- $\beta$ -TrCP	Skp1-Cul1-F- box ligase containing the F-box protein $\beta$ -transducin repeat-containing protein ( $\beta$ TrCP)
SCID	Severe combined immunodeficiency
shRNA	Short-hairpin RNA
siRNA	Small interfering RNA
SIRT	sirtuin
SL1	selectivity factor-1
SLE	systemic lupus erythematosus
SNF2	sucrose non-fermentable 2 chromatin remodeller
SWI/SNF	SWItch/Sucrose nonfermentable
SWR	Swi2/Snf2-related ATPase
T1D	type 1 diabetes
TAF1A	TAF <sub>1</sub> 48
TAF1B	TAF <sub>1</sub> 63
TAF1C	TAF <sub>1</sub> 110
TAF1D	TAF <sub>1</sub> 41
TAFII250	TATA binding protein associated factor 250
TAFs	TBP-associated factors
TAP	Transporter associated with antigen presentation
TBP	TATA-box binding protein
TCR	T cell receptor
TET	ten-eleven-translocation
TGF- $\beta$	transforming growth factor beta
Th	T helper cell
TIF1A/B	transcription initiation factor 1A/B
TIMP-3	Tissue inhibitor of metalloproteinase 3
TNF- $\alpha$	Tumor necrosis factor alpha
TRBP	TAR RNA binding protein
TRD	target recognition domain
Treg	regulatory T cell
TrxG	tritorax group of proteins
TSA	trichostatin A
TSS	Transcription start site
TTF-I	transcription termination factor
UBF	upstream binding factor
UC	ulcerative colitis

UCE	upstream control element
UPE	upstream promoter element
vmiRNA	Viral miRNA
VPA	Valproic acid
vsr	very short repair
WRN	Werner's syndrome helicase
WSTF	Williams syndrome transcription factor
WT	Wild-type
YY1	Ying Yang Protein 1
ZBG	zinc-binding group