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Essays in Biochemistry

Epigenetics, Disease and Behaviour

Edited by H. J. Lipps, J. Postberg and D. A. Jackson

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Preface

During the last decades of the past century, unprecedented progress in DNA sequencing technologies culminated in completion of the hugely ambitious project to sequence the human genome. In defining the genetic blueprint of humankind, this clearly represented a landmark in biological endeavour. Moreover, the immensely rich data that was generated by the human genome project represents an invaluable resource that allows the prediction of likely gene products and analysis of gene mutations, which might have a profound impact for the treatment of disease. However, despite the undisputed importance of this resource, it is clear that sequence information alone is not sufficient to predict the conditions under which a particular gene might be transcribed or the cell types in which transcription might occur. This knowledge demands a highly detailed insight into the regulatory mechanisms that together control gene expression.

Gene expression in eukaryotes is regulated in a hierarchical fashion. Although DNA-binding factors and their interactions with the transcription machinery play a pivotal role in activating gene expression, it is clear that numerous other factors, such as DNA modifications, chromatin structure and even higher nuclear organization also play a role. Features such as these can pass from mother to daughter cells during cell proliferation and account for the propagation of information that determines patterns of gene expression in cells that have identical genetic information. Interestingly, this non-Mendelian inheritance of cell phenotype in cells with the same genetic heritage is widespread throughout evolution and has been well characterized in lower eukaryotic cells, such as ciliated protozoa.

The 'causal interactions between genes and their products, which bring the phenotype into being' were first recognized by C.H. Waddington in 1942 and called 'epigenetics'. Explicitly, epigenetic mechanisms provide a series of regulatory principles that define potentially stable and heritable changes in gene expression – and hence cell phenotype – without altering the genetic information that is encoded within DNA. Since the seminal recognition of the importance of epigenetic inheritance, numerous studies have explored how epigenetic regulation can be fundamental to the process of cellular differentiation. But at the same time, it is clear that in understanding how epigenetic regulation defines cell type it might also define changes in patterns of gene expression that correlate with alterations in behaviour and the onset of disease.

To this day, the study of epigenetics continues to reveal the complexity of regulatory mechanisms that control gene expression. Signals that trigger the early events in epigenetic programming typically involve differentiation cues that arise as primitive stem cells divide to form descendants that are committed to a specific developmental lineage. The trigger that drives a commitment to

differentiation might in turn result in the expression of DNA-binding factors or synthesis of non-coding RNA molecules, which initiate a series of events that ultimately dictate patterns of gene expression in progeny cells. As differentiation proceeds, the required patterns of gene expression are fixed and maintained by changes in DNA and chromatin that can be perpetuated during DNA replication and cell division. Mechanisms that contribute to this epigenetic programming of cell phenotype involve numerous pathways, which include: DNA methylation, post-translational histone modification, formation of chromatin with specialized histone variants, regulation of nucleosome positioning, as well as features that dictate the folding and organization of DNA inside the nucleus to facilitate or suppress gene expression.

There is no denying that the characteristic behaviour of all organisms, including humans, is determined by the genetic information that is stored within their DNA. However, there is a growing realization that the expression of this genotype can be modulated and influenced by external and/or environmental factors. In addition, because of the complexity of epigenetic mechanisms that control gene expression, it is clear that the links between genotype and phenotype can be much more dynamic than was previously thought to be the case. With this in mind, it was decided to publish a volume of *Essays in Biochemistry* on epigenetics, disease and behaviour. In commissioning this special volume, the editors set out to provide an up-to-the-minute perspective on epigenetic research that would appeal to both experts in related fields of chromatin biology and a more general readership that finds fascination in the mechanistic intricacies of biological systems.

Many intriguing and exciting research topics are covered in this volume and we are delighted that so many outstanding scientists working in the field of epigenetics each agreed to contribute. The early chapters of the volume give an overview of fundamental epigenetic mechanisms. The volume begins with two chapters that explore how the nuclear architecture of higher eukaryotes might have evolved to provide an environment that was amenable to epigenetic programming (Postberg et al. and Jackson). Given the complexity of their genomes and the huge variety of different cell types that they contain, it is no surprise that advanced eukaryotes have evolved a complex hierarchy of mechanisms to regulate the expression of their genes. The concept of spatial or architectural epigenetics describes how the folding and packaging of DNA inside nuclei contributes to the regulation of gene expression by defining environments that allow or suppress gene function. Three chapters that follow explore how very local features of chromatin architecture can be imposed on this global nuclear organization. The first (Winter and Fischle), looks in detail at how post-translational histone modifications and DNA methylation provide complex, combinatorial mechanisms for fixing patterns of gene expression that define cell fate. However, even when heritable epigenetic patterning has been established, mechanisms must exist to ensure that the appropriate genes can be accessed to facilitate their expression. During this process, the dynamic properties of chromatin

are defined by the activity of nucleosome remodelling enzymes (Korber and Becker), which allow nucleosomes to reposition along the DNA. Interestingly, while nucleosome repositioning might appear to contradict the basic premise of epigenetic programming, the mechanisms of regulation have been shown to control differential folding of the chromatin fibre and maintain the organization of heritable epigenetic structures. The incorporation of specialized histone variants into chromatin provides an additional mechanism for stabilizing the epigenetic code (Ray-Gallet and Almouzni) and recent studies are beginning to explain how specialized histone H3 variants can be deposited on to DNA by histone chaperones and transmitted or removed during epigenetic programming.

Following on from the discussion of chromatin-based mechanisms, two chapters discuss the relevance of RNA for epigenetic regulation. While Mochizuki describes the function of snRNA (small nuclear RNA) in the regulation of DNA rearrangements in a ciliate model system, Cuzin and Rassoulzadegan discuss the role of gametic RNAs as epigenetic regulators. Finally, epigenetic markers are very dynamic and this is most relevant for the control of the cell cycle (Bou Kheir and Lund). Crucially, cell-cycle progression demands the structured timing of events that control the activity of gene transcription and epigenetic mechanisms that dictate the accessibility of DNA. Chromatin modifiers are known to regulate cell-cycle progression by controlling temporal gene expression and local chromatin structure in order to ensure that daughter cells, which form during cell division, inherit the correct epigenetic information.

In recent years it has become clear that epigenetic mechanisms play a major role in many serious human diseases (Hajji and Joseph, Ye et al., Silahtaroglu and Stenvang, Hirasawa and Feil, and Rudenko); key examples are described here in order to emphasize fundamental features of epigenetic programming. The development of cancer, for example, is known to involve multiple changes in gene expression, which might often involve defects in epigenetic regulation. Cell death by apoptosis provides a regulatory failsafe that restricts the early stages of tumour formation, and defects in the epigenetic regulation of these pathways correlate with the emergence of cancer, allowing the exciting possibility of developing epigenetic therapies (Hajji and Joseph). In addition, defects in telomere function and related early stages of chromosome instability (Ye et al.) and alteration in microRNA-based epigenetic regulatory mechanisms (Silahtaroglu and Stenvang) can also be discussed in the context of the initiation and progression of human diseases, but most notably cancer. Defects in epigenetic programming correlate with the wide-spread alterations in gene expression that are seen in many cancers. However, much more specific diseases arise from profound defects in epigenetic programming. Perhaps the most extreme examples arise from defects in genomic imprinting (Hirasawa and Feil). Imprinting provides a mechanism of regulating gene expression during development and imprinted genes are controlled so that the expression from either the male or female gamete is dramatically restricted. The regulatory mechanism involves DNA methylation

within genetically defined imprinting control regions and defects in the process are known to be causally involved in several human diseases.

Many other model systems also provide paradigms for exploring the importance of epigenetic mechanisms in regulating gene expression. The trypanosome *Trypanosoma brucei* is a unicellular parasite which causes African sleeping sickness. Many aspects of the biology of this organism have unusual features with epigenetic control and it is clear that much more detailed understanding of epigenetic regulation will be needed to understand how the different regulatory layers contribute to the spread of disease. The multi-layered characteristic of epigenetic regulation is also evident in the control of V(D)J recombination (Johnson et al.), a process that breaks, rearranges and repairs specific genetic loci to generate a vast repertoire of antigen receptor proteins. The formation of double-strand breaks in DNA is inherently risky and, to mitigate disaster, recombination is carefully controlled at various levels, which include chromatin conformation and nuclear architecture.

To complete the volume, three chapters discuss how epigenetic programming is involved in different aspects of development. In the first of these chapters, Melcer and Meshorer discuss how chromatin plasticity in pluripotent cells contributes to the process of cell commitment and differentiation. At much later stages of human development, the post-translational modification of chromatin proteins and DNA methylation, which regulate gene activity in the central nervous system, provide a pivotal role in synaptic plasticity and memory formation (Roth et al.). Finally, the influence of the environment on the epigenome is discussed (McGowan and Szyf) and models developed to explore whether changes in epigenetic programming could mimic the behaviour of genetic polymorphisms and how these might have an impact on the development of disease, with particular focus on mental health in adulthood.

In summary, the present *Essays in Biochemistry* volume provides an up-to-date appraisal of the fundamental principles that facilitate the epigenetic regulation of chromatin function. In describing the key molecular principle, particular attention has been placed on the use of appropriate model systems that emphasize the relevance of epigenetics in human diseases and behaviour. The study of epigenetic regulation is clearly relevant to our understanding of basic biological processes that dictate chromatin function. But in addition, we are deeply convinced that, in the future, a detailed understanding of epigenetic principles will be essential for the treatment of human diseases and for developing safe and reproducible gene and stem cell therapies. Thinking esoterically, it is even exciting to imagine how future developments in epigenetic research might inform such disparate socio-economic disciplines as pedagogics, economic and even politics.

The editors would like to thank Portland Press staff, in particular Clare Curtis, for their efficient work in producing this volume.

Hans Lipps, Jan Postberg and Dean Jackson
June 2010

Authors

Jan Postberg studied in Bochum, Witten/Herdecke and as a visiting student in Santiago de Compostela. He worked as a post-doc in the laboratory of Hans Lipps in Witten/Herdecke and with Thomas Cremer at the LMU (Ludwig-Maximilians-University), Munich. He is now project leader in the research laboratory of the Pediatrics Center at the HELIOS Klinikum Wuppertal (Stefan Wirth). **Hans Lipps** studied in Tübingen and Edinburgh. As a post-doc and after his habilitation he worked at the Institute of Cell Biology in Tübingen, at the Institute of Animal Genetics, Edinburgh, the MRC Laboratory of Molecular Biology, Cambridge, the Department of Cellular and Developmental Biology, Boulder, Colorado, and the Department of Cellular Biology, Rome. In 1995 he built-up the Chair of Cell Biology at the University of Witten/Herdecke (UWH). Since 2010 he has been head of the Center for Biomedical Education and Research (ZBAF) at the UWH. **Thomas Cremer** studied in Freiburg and Göttingen. As a post-doc he worked in Heidelberg, in Irvine, California, at Yale University, New Haven, and at Washington University in St Louis, Missouri. Since 1996 Thomas Cremer has held the Chair of Anthropology and Human Genetics at the LMU, Munich.

Dean Jackson obtained a B.Sc. in Biochemistry at the University of Manchester in 1976 and his Ph.D. in the same department under Professor Geoff Barker. He subsequently moved to the Dunn School of Pathology at the University of Oxford where he published a series of experiments on structure–function links in the nuclei of human cells. With Peter Cook and other collaborators, these seminal studies included analysis of the structure of sites of RNA synthesis at the nucleoskeleton, analysis of chromatin loops, visualization of the core filaments of the nucleoskeleton, the characterization or transcription and replication factories, and characterization of chromosomal DNA foci. Having moved to Manchester in 2000, he is now a senior lecturer in the Faculty of Life Sciences at the University of Manchester. His present interests include the role of nuclear and chromosome structure in regulating DNA and RNA synthesis, and molecular mechanisms that regulate genome stability in human cells.

Since August 2009, **Stefan Winter** has been a post-doc with Wolfgang Fischle at the Max-Planck Institute for Biophysical Chemistry (Göttingen, Germany). From 1999 to 2004, he studied Microbiology and Genetics at the University of Vienna, Austria. His graduate studies were from 2003 to 2004 in the laboratory of Christian Seiser (Medical University of Vienna, Austria), where he also carried out his Ph.D. (from 2004 to 2008). Prior to his current position, he was a post-doc with Gustav Ammerer (MFPL Laboratories,

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Philipp Korber did his Ph.D. in 2000 with Rainer Jaenick (University of Regensburg, Germany), and James C.A. Bardwell (University of Michigan, Ann Arbor, U.S.A.). From 2000 to 2005 he carried out postdoctoral studies with Wolfram Hörz (Adolf-Butenandt-Institute, University of Munich, Germany). Since 2006 he has been Principal Investigator at the Adolf-Butenandt-Institute. He is a NET member of the Network of Excellence 'The Epigenome'. **Peter Becker** did his Ph.D. in 1987 with Günther Schütz (German Cancer Research Center). He carried out postdoctoral studies with Carl Wu (National Cancer Institute, National Institutes of Health, Bethesda, MD, U.S.A.). From 1991 to 1999 he was group leader of the Gene Expression Programme at EMBL. Since 1999 he has been Professor of Molecular Biology at the LMU in Munich. He is an elected member of EMBO and the German Academy of Sciences, Leopoldina. In 2005 he received the Gottfried-Wilhelm Leibniz Award of the Deutsche Forschungsgemeinschaft.

Dominique Ray-Gallet is a Institut National de la Santé et de Recherche Médicale (INSERM) researcher in the laboratory of Geneviève Almouzni. **Geneviève Almouzni** is a Centre National de la Recherche Scientifique (CNRS) director and head of the 'Nuclear dynamics and genome plasticity' department at the Curie Institute, Paris, France. The unifying theme that underlies her work is the wish to understand the principles that govern nuclear organization, and the functions and co-ordination of these events to ensure the maintenance of cellular identity throughout cell divisions.

Kazufumi Mochizuki obtained his Ph.D. from the Graduate University for Advanced Studies (Hayama, Japan) in 2000. He joined the laboratory of Professor Martin A. Gorovsky at the University of Rochester (Rochester, NY, U.S.A.) as a postdoctoral research fellow in 2001. Since 2006, he has been a group leader at the Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA, Vienna, Austria). His research interests are in the regulation of chromatin structure by non-coding RNAs.

François Cuzin is Emeritus Professor at the University of Nice and is a member of the French Academy of Sciences, EMBO and Academia Europaea. He did his Ph.D. under the supervision of François Jacob from 1961 to 1966. He then went on to do postdoctoral work in the laboratory of Paul Berg at Stanford University. From 1970 to 1974 he was group leader at the Institut

Pasteur Paris, from 1975 to 1981 was group leader of the CNRS Institute Centre de Biochimie (Nice), and was Director of the Inserm Research Unit (Nice) from 1982 to 2003. **Minoo Rassoulzadegan** was Attache de Recherche and the Charge de Recherche (CNRS) from 1979 to 1985. Since 1986 she has been Directeur de Recherche (CNRS), and since 2004 has been Directrice of the UMR 636 Inserm. She is a member of EMBO and is involved in a number of national committees, including Agence Nationale de la Recherche and Commision Epigenetique de l'Inserm.

Tony Bou Kheir obtained a B.Sc. in Molecular Biology at the Saint-Joseph University, Beirut, Lebanon, in 2005. He completed his masters training in the laboratory of Robert Feil at the Institute of Molecular Biology (IGMM), Montpellier, France, in 2007 studying the effect of a non-coding RNA truncation on the epigenetic regulation of the imprinted Kcnq1 domain in the mouse. He is currently doing his Ph.D. studies at the Biotech Research and Innovation Centre, University of Copenhagen, in the laboratory of Anders Lund working on epigenetic modifications across the cell cycle and microRNA-mediated cancer-gene regulation. **Anders Lund** is a Professor at the Biotech Research and Innovation Centre, University of Copenhagen. His research group works on epigenetics and microRNA-mediated gene regulation, both of which are studied in the context of cancer development. He obtained his Ph.D. from the University of Aarhus, Denmark, studying retroviral replication. He did the majority of his postdoctoral work in the group of Professor Maarten van Lohuizen at the Netherlands Cancer Institute in Amsterdam studying epigenetic regulators and identifying cancer-relevant genes in the mouse using retroviral insertional mutagenesis. He returned to Denmark in 2004 to establish his own research group and became full Professor in 2009.

Nabil Hajji is currently a lecturer in Toxicology at Imperial College, London. He obtained his Ph.D. in molecular and cell biology at Seville University, Spain. He held his first postdoctoral appointment at Macarena Hospital, Seville. Subsequently, he held postdoctoral appointments at the Karolinska Institutet in Stockholm, Sweden, at the Institute of Cancer Studies at Birmingham University, U.K., and at the Centre for Cutaneous Research at the Institute of Cell and Molecular Science at Barts and The London. His research has been primarily focused on the study of the anticancer activity of natural products and the assessment of potential new pharmacological drugs. The second line of his Ph.D. investigation was the study of environmental fate, ecotoxicology and human health concerns (follow-up analysis of genotoxic damage). After completing his Ph.D., he pursued several postdoctoral studies where he has developed expertise in epigenetics and programmed cell death in areas such as diabetes, cancer and neurodegenerative diseases. His current area of interest/expertise includes different aspects of epigenetic alterations by environmental contaminants and disease risk. **Bertrand Joseph** is Associate

Professor of Cell and Molecular Biology at the Cancer Centrum Karolinska and is affiliated to the Karolinska Institutet, Sweden. He holds a Ph.D. degree in Medical Sciences from the University of Sciences and Technologies of Lille, France. He did his postdoctoral training at the Institute of Environmental Medicine, Karolinska Institutet, Sweden, and the Ludwig Institute for Cancer Research, Stockholm branch, Sweden. At present, his general research interests are focused on the genetic and epigenetic molecular mechanisms regulating cell death/survival decisions. His group has made notable contributions to the characterization of cell death mechanisms that are involved in the elimination of cancer cells.

Jing Ye is a Doctor of Internal Medicine at Shanghai Ruijin Hospital, Shanghai, affiliated to the School of Medicine, Shanghai Jiaotong University, China; Assistant Professor in the School of Medicine, Shanghai Jiaotong University, China; and a postdoctoral fellow in Professor Eric Gilson's team, working on telomeric chromatin and signalling. **Yunlin Wu** is a Doctor of Digestive Medicine, Shanghai Ruijin Hospital, Shanghai, affiliated to the School of Medicine, Shanghai Jiaotong University, China; Director of the Gastrointensive and Herpetological Department at Shanghai Ruijin Hospital; and Professor in the School of Medicine, Shanghai Jiaotong University, China. **Eric Gilson** is Professor of Cell Biology, University and Faculty of Medicine, Nice, France, Director of the 'Laboratory of Biology and Pathology of Genomes' at the Faculty of Medecine of Nice, and team leader in the field of telomere, chromatin and cancer since 1994. His main achievements are his contribution to the discoveries of the protein counting model of telomere length regulation, the role of spatial distribution of telomere protein in gene regulation and of the human telomeric proteins TRF1, TRF2 and Apollo.

Asli Silahtaroglu is an Associate Professor at the University of Copenhagen, Department of Cellular and Molecular Medicine, Wilhelm Johannsen Centre for Functional Genome research. She has a bachelor degree in Biomedical Sciences from Istanbul University and a masters [M.Sc. (Med. Sci.)] degree in Medical Genetics from Glasgow University. She received her Ph.D. degree in Medical Biology (major in Genetics) from Istanbul University Institute of Health Sciences with her work on fluorescence *in situ* hybridization on human female meiotic chromosomes which was performed in the Kennedy Institute in Denmark. Her scientific interests are in methods of *in situ* hybridization, non-coding RNAs, epigenetics and chromosomal rearrangements. Based on a Ph.D. and 7 years of postdoctoral experience in cancer research, **Jan Stenvang** has moved from the initiation of frontline research to leading R&D-based research groups in academia and industry, coordination of international projects and collaborations. He obtained his Ph.D. at the Danish Cancer Society, focusing on endocrine resistance in breast cancer model systems and application of locked nucleic acid as antisense molecules.

As a post-doc, he has initially investigated molecular mechanisms involved in anti-oestrogen resistance in breast cancer cells. Subsequently, he has worked on various aspects of microRNA and cancer, especially focusing on the silencing of microRNAs by anti-miRs as a potential therapeutic strategy. Recently, he has initiated cancer biomarker projects aimed at detection of early phases of cancer by either microRNA detection or by multiplex protein detection.

Ryutaro Hirasawa obtained his Ph.D. degree at the Graduate University for Advanced Studies (Sokendai) in Japan, in 2007, and was a postdoctoral research fellow at the National Institute of Genetics (NIG) in Mishima, Japan, where he investigated the roles of DNA methyltransferases in genomic imprinting control. In 2008, he became a postdoctoral researcher at the Institute of Molecular Genetics (IGMM) in Montpellier, France. His research interests include the epigenetic regulation of genomic imprinting, particularly the cross-talk between DNA methylation and covalent histone modifications.
Robert Feil graduated at the University of Wageningen, the Netherlands. In 1991 he obtained a Ph.D. degree in human genetics at the IGBMC in Strasbourg, France. He became postdoctoral fellow and then group leader at the Babraham Institute in Cambridge, U.K., where he explored the regulation of DNA methylation. In 2001, he moved his research to Montpellier, France. His team has been using the mouse as a model system and explores the regulation of chromatin in imprinting and development. They are particularly interested in the mechanisms underlying the pathological deregulation of epigenetic imprints.

Gloria Rudenko studied Biochemistry at the University of Leiden, the Netherlands, before doing Ph.D. research in the Department of Genetics, Columbia University, New York. After returning to the Netherlands for postdoctoral research in the Netherlands Cancer Institute in Amsterdam, she became a Wellcome Senior Fellow in the Basic Biomedical Sciences in the Department of Biochemistry (Peter Medawar Building for Pathogen Research) at the University of Oxford. Her research group is currently located in the Division of Cell and Molecular Biology at Imperial College London. Here they investigate the molecular mechanisms underpinning antigenic variation in the African trypanosome *Trypanosoma brucei*.

Kristen Johnson received her Ph.D. in 2005 from Columbia University. Her Ph.D. was performed in the laboratory of Dr Kathryn Calame where she worked on the epigenetic regulation of immunoglobulin heavy-chain recombination during B-cell development. She then spent 2 years in the laboratory of Dr Harinder Singh at the University of Chicago as a postdoctoral fellow under the support of the Leukemia and Lymphoma Society. While with Dr Singh, she studied the role of temporally regulated signalling pathways in guiding developing B-cells through the pre-B-cell stage and the initiation of light-chain recombination. Her later work was done in collaboration with Dr Jane Skok.

In a desire to expand her technical expertise and continue to explore their common interests, Kristen joined the laboratory of Dr Jane Skok at New York University School of Medicine in 2008. **Julie Chaumeil** received her Ph.D. in 2006 from the University Paris XI-Orsay, France. Her Ph.D. was performed in the laboratory of Dr Edith Heard at the Curie Institute where she worked on the epigenetic regulation of X chromosome inactivation during mammalian female development. She then spent 18 months in the laboratory of Professor Jennifer Graves at the Australian National University as a postdoctoral fellow working on the evolution of X chromosome inactivation across mammals. Having always been interested in understanding how chromatin changes and nuclear organization are involved in regulation of gene expression, she is now working in the laboratory of Dr Jane Skok at New York University School of Medicine focusing on the epigenetic regulation of T-cell receptor gene recombination during T-cell development. **Jane Skok**'s laboratory uses sophisticated microscopic techniques to visualize recombination in individual cells, tracing the dynamic changes in chromosome architecture and nuclear location at different stages of this complex process. This line of research unites two lifelong passions: science and art. After completing her Ph.D. in Immunology and Genetics at the Imperial Cancer Research Fund in Lincoln's Inn Fields, London, Dr Skok pursued her lifelong interest in art, while caring for her young children. After a 10-year gap she returned to science, joining David Gray's laboratory at Imperial College London as a postdoctoral fellow to study B-cell biology and subsequently in Mandy Fisher's laboratory acquiring expertise in understanding how nuclear organization of the antigen receptor genes regulates V(D)J recombination and allelic exclusion. She continued to pursue these questions in her own laboratory at University College London and elucidated the roles of Pax5, locus contraction and nuclear subcompartmentalization in maintaining allelic exclusion. In 2006 Dr Skok was recruited to New York University School of Medicine, where her laboratory has revealed the activities of several signalling factors in guiding B-cell development. Most recently the Skok laboratory made the surprising discovery that the RAG proteins and the DNA-damage-response factor ATM help ensure allelic exclusion at the immunoglobulin gene loci. Their wider interests include understanding how gene interactions between key loci co-ordinate their expression profiles in a way that contributes to lineage commitment.

Eran Meshorer joined the Department of Genetics at the Alexander Silberman Institute of Life Sciences, Hebrew University, in 2007 and heads the Stem Cell Chromatin Laboratory. Before returning to Jerusalem, he spent 4 years as a postdoctoral fellow at the National Cancer Institute, National Institutes of Health. His research focuses on single-cell and genome-wide approaches to understand chromatin plasticity in embryonic and neuronal stem cells and during stem cell differentiation and reprogramming, with particular

emphasis on epigenetic regulation. Major recent contributions include the discovery that chromatin in undifferentiated embryonic stem cells is substantially more plastic and dynamic than in differentiated cells, as well as finding the epigenetic-related mechanisms by which this plasticity is maintained and some of the key proteins that contribute to open chromatin in embryonic stem cells. The Meshorer group established close collaboration with leading experimental and computational groups in the U.S., Europe and Israel, towards an integrative approach to the study of chromatin and epigenetic regulation in stem cells. By combining sophisticated imaging techniques at the single-cell level and genome-wide approaches, the Meshorer group aims to provide deep understanding of chromatin-related regulation in stem cells and reprogramming. **Shai Melcer** is a Safra Fellow graduate student in the laboratory of Eran Meshorer in the Department of Genetics at the Alexander Silberman Institute of Life Sciences, Hebrew University. Current work includes delineating the molecular mechanisms of chromatin plasticity in embryonic stem cells. Shai obtained his M.Sc., also at the Department of Genetics, working on the nuclear envelope and the nuclear lamina in *Caenorhabditis elegans.*

Tania Roth received her bachelor's degree in biology from Roanoke College and her Ph.D. in zoology from The University of Oklahoma. She did her postdoctoral training with Dr David Sweatt at Baylor College of Medicine and The University of Alabama at Birmingham. In Dr Sweatt's laboratory, her research focused on the role of DNA methylation in learning and memory. She is currently an Assistant Professor in the Department of Psychology at the University of Delaware, and her research focuses on defining epigenetic mechanisms responsible for environmental influences on CNS (central nervous system) gene activity, development of behaviour and psychiatric disorders. **Eric Roth** received his Ph.D. in Zoology from The University of Oklahoma. He did his postdoctoral training at The University of Texas Medical School with Dr James Knierim and at The University of Alabama at Birmingham with Dr David Sweatt. As a postdoctoral fellow in Dr Sweatt's laboratory, his research focuses on the role of epigenetic mechanisms, particularly DNA methylation, in spatial learning and memory. Other research interests include applying integrative ecological and neurobiological approaches to understand spatial ecology, animal cognition and conservation. **J. David Sweatt** received his Ph.D. in pharmacology from Vanderbilt University. He did his postdoctoral training at Columbia University with the Nobel Laureate Dr Eric Kandel. He is currently Chair of the Department of Neurobiology and Director of the Evelyn F. McKnight Brain Institute at the University of Alabama at Birmingham. Dr Sweatt's research focuses on molecular mechanisms, including epigenetic mechanisms, underlying learning and memory. He uses molecular, electrophysiological and behavioural approaches to understand signal transduction mechanisms in the hippocampus facilitating memory, as

well as genetically engineered mouse models of human cognitive disorders to investigate the molecular basis of memory dysfunction.

Moshe Szyf is a James McGill and GlaxoSmithKline Professor in the Department of Pharmacology and Therapeutics at McGill University in Montreal, Quebec, Canada. **Patrick McGowan** is a postdoctoral fellow in the Department of Psychiatry at McGill University and the Douglas Mental Health Research Institute in Montreal, Quebec, Canada.

Abbreviations

A-gene	antigen gene
AHO	Albright's hereditary osteodystrophy
ALL	acute lymphoblastic leukaemia
ALS	amyotrophic lateral sclerosis
ALT	alternative lengthening of telomeres
AML	acute myeloid leukaemia
Apaf-1	apoptotic protease-activating factor 1
Arp4	actin-related protein-4
ART	assisted reproduction technology
AS	Angelman syndrome
ATM	ataxia telangiectasia mutated
ATR	ataxia telangiectasia mutated- and Rad3-related
AUF1	ARE (AU-rich element)/poly(U)-binding/ degradation factor 1
Bcl-2	B-cell lymphoma protein-2
B-CLL	B-cell chronic lymphocytic leukaemia
BCR	B-cell receptor
Bdnf	brain-derived neurotrophic factor
BH	Bcl-2 homology
BRG1	brahma-related gene 1
BWS	Beckwith–Wiedemann syndrome
CBP	CREB [CRE (cAMP-response element)-binding protein]-binding protein
Cbs	chromosome breakage sequence
CDK	cyclin-dependent kinase
CENP-A	centromere protein-A
c-FLIP	cellular FLICE [FADD (Fas-associated death domain)-like IL (interleukin)-1β-converting enzyme]-inhibitory protein
Chd1	chromodomain-helicase-DNA-binding protein 1
ChIP	chromatin immunoprecipitation
CHK2	checkpoint kinase 2
CNS	central nervous system
CRC	colorectal cancer
CRE	cAMP-response element
CREB	CRE (cAMP-response element)-binding protein
CST	Cdc13-Stn1-Ten1

CTCF	CCCTC-binding factor
CT	chromosome territory
D	diversity
DAPK	death-associated protein kinase
DcR1	decoy receptor 1
DISC	death-inducing signalling complex
DMR	differentially methylated region
DN	double-negative
DNA-FISH	DNA fluorescence *in situ* hybridization
DNMT	DNA methyltransferase
DP	double-positive
DSB	double-strand break
DSD	DNA-synthesis-dependent
DSI	DNA-synthesis-independent
ER	endoplasmic reticulum
ERK	extracellular-signal-regulated kinase
ES	expression site
ESAG	expression-site-associated gene
ESB	expression site body
ESC	embryonic stem cell
Ezh2	enhancer of zeste homologue 2
FADD	Fas-associated death domain
FasL	Fas ligand
FDA	Food and Drug Administration
FISH	fluorescence *in situ* hybridization
FRAP	fluorescence recovery after photobleaching
GFP	green fluorescent protein
GI	gastro-intestinal
GNAT	Gcn5 *N*-acetyltransferase
GR	glucocorticoid receptor
GRB10	growth-factor-receptor-binding protein 10
GWAS	genome-wide association studies
HAT	histone acetyltransferase
HDAC	histone deacetylase
HDACi	HDAC inhibitor
HDM	histone demethylase
HIC1	hypermethylated in cancer 1
HKMT	histone-lysine *N*-methyltransferase
HJURP	Holliday junction-recognizing protein
HMT	histone methyltransferase
HOMedU	hydroxymethyluridine
HP1	heterochromatin protein 1

HPA	hypothalamic–adrenal–pituitary
HRMT	histone-arginine *N*-methyltransferase
hSWI/SNF	human switch/sucrose non-fermentable
hTERT	human TERT
IAP	inhibitor of apoptosis
IC	interchromatin compartment
ICD	interchromosome domain
ICM	inner cell mass
ICN	interchromatin network
ICR	imprinting control region
IES	internal eliminated sequence
IFN-γ	interferon γ
Ig	immunoglobulin
IGF2	insulin-like growth factor 2 (gene)
IL	interleukin
IMS	intermembrane space
ING	inhibitor of growth
INM	inner nuclear membrane
iPSC	induced pluripotent stem cell
J	joining
JMJD	JmjC-domain-containing demethylase
KDM	lysine demethylase
LCR	locus control region
LG	licking/grooming
LOH	loss of heterozygosity
LSD1	lysine-specific demethylase 1
LTP	long-term potentiation
MAPK	mitogen-activated protein kinase
MBD	methyl-DNA binding protein
MCL1	myeloid cell leukaemia sequence 1
MeCP2	methyl CpG-binding protein 2
MEF	mouse embryonic fibroblast
miRNA	microRNA
MLS	multi-loop subcompartment
MOMP	mitochondrial outer membrane permeabilization
MSK1/2	mitogen- and stress-activated kinase 1/2
Mst1	mammalian sterile twenty 1
Nap1	nucleosome assembly protein 1
NASP	nuclear autoantigenic sperm protein
NF-κB	nuclear factor κB
NFR	nucleosome-free region
NGFI-A	nerve growth factor-inducible protein A

NHEJ	non-homologous end-joining
NoRC	nucleolar remodelling complex
NPC	neuronal progenitor cell
Npm1	nucleophosmin 1
Pax5	paired box gene 5
PBA	4-phenylbutyric acid
P-bodies	processing bodies
PCD	programmed cell death
PCH	pericentromeric heterochromatin compartment
PCNA	proliferating-cell nuclear antigen
PDAC	pancreatic ductal adenocarcinoma
PHD	plant homeodomain
PHP	pseudohypoparathyroidism
PML	promyelocytic leukaemia
Pol	polymerase
POT1	protection of telomeres protein 1
PP1	protein phosphatase 1
PR	perichromatin region
pRb	retinoblastoma protein
PRC	Polycomb repressive complex
PRMT	protein arginine methyltransferase
pRNA	promoter RNA
PTEN	phosphatase and tensin homologue deleted on chromosome 10
PTH	parathyroid hormone
PTM	post-translational modification
PWS	Prader–Willi syndrome
Rad21	radiation-sensitive mutant 21
RAG	recombination-activating gene
(h)Rap1	(human) repressor activator protein
RbAp48	retinoblastoma-associated protein 48
RCC1	regulator of chromosome condensation 1
rDNA	ribosomal DNA
RHPS4	3,11-difluoro-6,8,13-trimethyl-8H-quino[4,3,2-kl]acridinium methosulfate
RISC	RNA-induced silencing complex
RNAi	RNA interference
RNAPII	RNA polymerase II
RNP	ribonucleoprotein
Rpd3	reduced potassium dependency 3
RPS6K	ribosomal S6 kinase
rRNA	ribosomal RNA

RSS	recombination signal sequences
SAHA	suberoylanilide hydroxamic acid
SAM	*S*-adenosyl-L-methionine
scn	scan
SET	Su(var)3–9, Enhancer of Zeste, Trithorax
siRNA	small interfering RNA
SIRT1	sirtuin 1
SRA	SET and RING finger-associated
SRS	Silver–Russell syndrome
ssDNA	single-stranded DNA
STAT	signal transducer and activator of transcription
SWI/SNF	switch/sucrose non-fermentable
TbISWI	*Trypanosoma brucei* ISWI (imitation-SWI protein)
TBP	TATA-binding protein
TbRAP1	*Trypanosoma brucei* RAP1
TCR	T-cell receptor
TERC	telomerase RNA component
TERRA	telomeric repeat-containing RNA
TERT	telomerase reverse transcriptase
TGFβ	transforming growth factor β
TNDM	transient neonatal diabetes mellitus
TNF	tumour necrosis factor
TNM	tumour, node, metastasis
TOPO I	topoisomerase I
TPE	telomere position effect
TPP1	three-prime phosphatase 1
TRAIL	TNF-related apoptosis-inducing ligand/Apo2L
TRF	telomeric-repeat-binding factor
TRFH	TRF homology
tRNA	transfer RNA
TSA	trichostatin A
UPD	uniparental disomies
UTR	untranslated region
V	variable
VRK1	vaccinia-related kinase 1
VSG	variant surface glycoprotein
XAF1	XIAP (X-linked inhibitor of apoptosis)-associated factor 1
YY1	Yin Yang 1