Epigenetics and Human Health

Walter Doerfler
Petra Böhm *Editors*

Epigenetics – A Different Way of Looking at Genetics

Springer

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Preface

With a long-term interest in basic research on the biological functions of **DNA methylation**, I have been organizing International Symposia on this and related topics over a period of more than 30 years, both in Köln and in Weissenburg, Germany. The 1981 Cologne Spring Meeting at the Institute of Genetics, University of Cologne, on *DNA Methylation and Genome Organization* may well have been the first international conference on this topic.

Cologne Spring Meeting 1981

DNA Methylation and Genome Organization. March 04–07, 1981.

Weissenburg Symposium 2001

Medicine and Molecular Biology. May 03–06, 2001.

Weissenburg Symposium 2004

DNA Methylation: An Important Genetic Signal: Significance in Biology and Pathogenesis. May 12–15, 2004.

Weissenburg Symposium 2007

Medicine at the Interface between Science and Ethics. May 30–June 01, 2007.

Weissenburg Symposium 2011

Epigenetics and the Regulation of Gene Expression. June 20–22, 2011.

Weissenburg Symposium 2014

Epigenetics—A Different Way of Looking at Genetics. September 14–17, 2014.

The Venue: Weißenburg in Bayern (its official name) is an old town dating back to Roman origins (about 90 A.D.) with a well-preserved medieval center. The town is located 60 km to the South of Nuremberg and 130 km to the North of Munich. Weissenburg is a Frankonian town of some 18,000 inhabitants with diversified

industrial enterprises. The town is situated close to the *Naturpark Altmühltal* and the *Fränkisches Seenland*. The *Kulturzentrum* (dedicated as such in 1983), the venue of our symposia, was founded in 1325 as a Monastery of the Carmelites by the Emperor *Ludwig der Bayer*. Participants of former Symposia in Weissenburg have emphasized the friendly atmosphere and the opportunity for informal scientific and personal interactions inside and outside the lecture hall.

For the **2014 Symposium**, we have been fortunate in assembling an international group of leaders in their fields some of whom had attended earlier Weissenburg Symposia. As an appendix to this volume, I have attached the program for the 2014 Fifth Weissenburg Symposium on *Epigenetics—A Different Way of Looking at Genetics*.

Why ***Epigenetics—A Different Way of Looking at Genetics*** as the title for the symposium and the book? The designation epigenetics—a misnomer, I submit—is widely used in the literature when referring to genetic phenomena, which are not due to mutations in one of the approximately 20,000–25,000 human genes. In most such instances in human genetics, alterations in regulatory functions have been identified to cause gene silencing and its functional consequences. In all organisms, the control of gene expression is based on the defined interaction of regulatory proteins with distinct nucleotide sequences. When these regulatory pathways are disturbed or incapacitated, by mutations, promoter methylation, histone modifications, or deletions of regulatory nucleotide sequences, they then become responsible for these epigenetic alterations. Hence, from a biochemical perspective, it is difficult to envisage fundamental differences in mutations in a nucleotide sequence encompassing a gene or a regulatory element. In the human genome, many such elements, which are not part of a gene, have now been mapped in locations in between genes, e.g., by the ENCODE project (The ENCODE Project Consortium 2012). For these reasons, the term *Epigenetics* appears rather artificial; hence, the title of the Weissenburg Symposium 2014 has been deliberately chosen to allude to, and at the same time, challenge the use of this still "popular" phrase.

In contrast to prokaryotic organisms, the more complex eukaryotic genomes exhibit much larger nucleotide sequences with repetitive elements and retrotransposon insertions. A considerable portion of these repetitive sequences is actively transcribed into noncoding RNAs of largely unknown function. Many of these sequences carry important regulatory elements. The discovery of the repetitive sequences has in the "distant past" led to the unscientific claim that this "excess DNA" might be devoid of function. For years, the term "junk DNA" has been floated and vehemently discussed among adherents of the pros and cons of this, as is obvious now, completely unjustified term. Even then, one has often reasoned that evolution and conservation of energy in biology would not have allowed this enormous waste of energy during the replication and transcription of allegedly superfluous DNA sequences. Today, it is hard to comprehend how this erroneous concept could have found credence at all.

The field of **epigenetic mechanisms in biology** comprises a wide scope of research interests aimed at elucidating the regulation of genetic activities under many different conditions in cells and organisms across the entire spectrum of

biology and medicine. One way of explaining the significance of this genetic discipline is to remind ourselves of the apparent paradox that the chimpanzee and even the mouse have about the same number of an almost identical or at least very similar set of genes as humans. For a logical account for the obvious diparities between these species, it is useful to recall the differences in the ways they control gene activities during development and in postnatal life under the huge gamut of environmental conditions and their variabilities. The biochemical mechanisms responsible for epigenetic functions are only partly understood. A first important contribution came from studies on DNA methylation, i.e., from modifications of the genome itself, which were in due course followed by the realization that modifications of the DNA-binding histones, and probably of many additional DNA-binding proteins, play an important role in affecting genetic activities. Additionally, small RNAs contribute to the enormous repertoire of regulatory mechanisms in many different ways.

Epigenetics in all fields of biology and medicine. Thus, it has not been surprising that an increasing number of human diseases, many of them with proven or indirectly suggested genetic causation, could be attributed to epigenetic alterations in the absence of classical mutations in any of the genes possibly related to these diseases. Today, it is general knowledge that many of the common diseases, among them the neoplasias, can be causally linked to epigenetic alterations. The field has become huge. When interrogating PubMed, e.g., for *Epigenetics and Cancer*, thousands of hits are scored. Another fascinating realm of research has been opened by asking age-old questions about the influence of the environment on the genome via epigenetic mechanisms (Szyf 2012). Nowadays, PubMed interrogations offer far more than 1000 publications dealing with this important topic. Similarly, contributions of epigenetic research to the study of the highly complex psychiatric diseases have constantly increased in number and quality (Labrie et al. 2012).

Hence, when we set out to organize this Symposium on *Epigenetics*, we had to consider inviting researchers from many different fields in biology and medicine, and one meeting could not possibly attempt to cover all these aspects in depth. As will be apparent from a look into the program, we have been fortunate to attract many of the leaders in the fields. The main **areas in epigenetics** which were among the topics at the Fifth Weissenburg Symposium and are also reflected in this book's chapters have been the following:

Epigenetic Mechanisms
Epigenetics and Development
Complex Diseases
Tumor Biology
Immunology, Virology
Regulatory Systems

Thanks and acknowledgments are due to the members of the advisory board who have helped in selecting the speakers—Dirk Eick, München, Bernhard

Fleckenstein, Erlangen, Christoph Plass, Heidelberg, Andreas Radbruch, Berlin, Jörn Walter, Saarbrücken.

It is also a pleasure to recognize financial support for the Symposium by the Fritz Thyssen Stiftung, Köln (Az. 30.14.0.033); the DKFZ Cross Program Topic "epigenetics@dkfz"; DFG in Heidelberg, Priority Program, SPP1463 "Epigenetic Regulation of Normal Hematopoiesis and its Dysregulation in Myeloid Neoplasia," Heidelberg/Freiburg; the Institute of Clinical and Molecular Virology, University Erlangen-Nürnberg; the SFB 1064 (Chromatin Dynamics), München; Grünenthal GmbH, Aachen; Qiagen, Hilden; and last but not least Takara Bio Europe S.A.S.

Erlangen, Germany Walter Doerfler
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Szyf M. The early-life social environment and DNA methylation. Clin Genet. 2012;81:341–9.

Labrie V, Pai S, Petronis A. Epigenetics of major psychosis: progress, problems and perspectives. Trends Genet. 2012;28:427–35.

The Fifth Weissenburg Symposium Biriciana

Epigenetics—A Different Way of Looking at Genetics (September 15–17, 2014)

Venue: Kulturzentrum Karmeliterkirche Weißenburg in Bayern

Program and Organization

Walter Doerfler, Universität Erlangen-Nürnberg und Universität zu Köln

Advisory Board

Dirk Eick, Helmholtz Zentrum München
Bernhard Fleckenstein, Universität Erlangen-Nürnberg
Christoph Plass, Deutsches Krebsforschungszentrum Heidelberg
Andreas Radbruch, Rheumazentrum Berlin
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Institut für Virologie Erlangen
SFB 1064 München (Chromatin Dynamics)
Grünenthal GmbH, Aachen
Qiagen, Hilden
Takara Bio Europe S.A.S.

Program

Monday, 15 September

08:00–08:30 Opening—
Walter Doerfler—*Welcome to the Meeting and Introduction*
Jürgen Schröppel, Oberbürgermeister, Weißenburg—*Welcome to the Town*

Session I: Mechanisms

Chair Bernhard Fleckenstein, Erlangen

08:30–09:00 **Stephan Beck**, University College London
Insights from Methylome Analysis
09:00–09:30 **Dirk Schübeler**, Friedrich Miescher Institut, Basel
Setting and Reading DNA Methylation
09:30–10:00 **Michelle Débatisse**, Institut Curie, Paris
Respective Roles of Replication and Transcription in Common Fragile Site of Instability

10:00–10:30 Break
10:30–11:00 **Asli Tolun,** Boğaziçi Üniversitesi, Istanbul
Disease Gene Search
11:00–11:30 **Jörn Walter**, Universität des Saarlandes, Saarbrücken
Epigenomics of Primary Human Cells – New Insights in Epigenome Organization
11:30–12:00 **Josep Casadesús**, Universidad de Sevilla
Formation of Bacterial Lineages by Epigenetic Mechanisms
12:00–14:00 Lunch Break

Session II: Development

Chair Peter Jones, Grand Rapids, Michigan

14:00–14:30 **Andreas Radbruch**, Rheumazentrum, Berlin
Epigenetic Imprinting of Immunological Memory
14:30–15:00 **Moshe Szyf**, McGill University, Montreal, Quebec
DNA Methylation, Gene Expression Programing, and Behavior
15:00–15:30 **Alexander Meissner**, Harvard University, Boston, MA
DNA Methylation Dynamics in Stem Cells and Development
15:30–16:00 Break
16:00–16:30 **Rolf Ohlsson**, Karolinska Institutet, Stockholm
H3K9 Methylation Fine-tunes Coordination of Transcription by Regulating the Conformational Plasticity of Chromosomal Folding
16:30–17:00 **Ingrid Grummt**, DKFZ, Heidelberg
Non-coding RNA Controls Epigenetic Processes
17:00–17:30 **Robert Feil**, Institut Génétique Moléculaire, Montpellier, France
Role of Non-coding RNA Expression in Mammalian Genomic Imprinting

Tuesday, 16 September

Session III: Complex Diseases

Chair Andreas Radbruch, Berlin

08:30–09:00 **Andy Feinberg**, Johns Hopkins University, Baltimore, MD
The Epigenetic Basis of Common Human Disease
09:00–09:30 **Manel Esteller**, Universidad de Barcelona
Epigenetics in Health and Disease
09:30–10:00 **Giovanni Neri**, Università Catolica, Rome
What Mechanisms Induce Methylation of a FMR1 Full Mutation? A Still Unanswered Question

10:00–10:30 **Walter Doerfler**, Institute for Virology, Universität Erlangen-Nürnberg
Destabilization of the Human Epigenome by Foreign DNA Insertions
10:30–11:00 Break
11:00–11:30 **Juha Kere**, Karolinska Institutet, Stockholm
Methylation Studies in Complex Disorders: the Example of Asthma
11:30–12:00 **Arturas Petronis**, Krembil Epigenetics Laboratory, Toronto
A Comprehensive Search of epiSNPs in Major Psychosis: Insights for GWAS
12:00–14:00 Lunch Break

Session IV: Tumor Biology

Chair Stephan Beck, London

14:00–14:30 **Peter Jones**, Van Andel Institute Grand Rapids, Michigan
Gene Body Methylation Requires DNMT3B and is a Therapeutic Target for Genes Up-regulated in Cancer
14:30–15:00 **Ingemar Ernberg**, Karolinska Institutet, Stockholm
Epigenetics of EBV-Infection and Associated Diseases
15:00–15:30 **Michael Lübbert**, Universitätsklinikum, Freiburg
Recent Advances in the Treatment of Leukemia and Preleukemia Using Chromatin-modifying Agents: in vitro and in vivo Models
15:30–16:00 Break
16:00–16:30 **Christoph Plass**, DKFZ, Heidelberg
Epigenetic Reprogramming in Cancer
16:30–17:00 **Frank Rosenbauer**, Universitätsklinikum, Münster
Control of PU.1 Expression by Three-dimensional Chromatin Architecture in Hematopoiesis and Leukemia
17:00–17:30 **Jun Huh**, U. Mass. Medical School, Worcester, MA
Regulation of DNA Methylation Dictates Cd4 Gene Expression During Development of Helper and Cytotoxic T Cell Lineages
17:30–18:00 **Anita Göndör**, Karolinska Institutet, Stockholm
PARP1 and CTCF-mediated Interactions between Active and Inactive Chromatin Domains Regulate Circadian Transcription

For our Enjoyment and Recreation

18:15–19:30 ***"Musica Romana"*—Justus Willberg**, Director of the Weissenburg School of Music presents
Music and Instruments from the Time of the Roman Biriciana (third century of our time)
20:00 **Symposium Dinner**
Gasthof "Goldener Adler"

Wednesday, 17 September

Session V: Immunology, Virology

Chair Michelle Débatisse, Paris

08:30–09:00 **Yuka Kanno**, National Institutes of Health, Bethesda, MD
Lymphocyte Identity and Genomic Switching
09:00–09:30 **Christoph Niehrs**, Universität Mainz
TARID lncRNA Directs Demethylation and Activation of the Tumor Suppressor TCF21 via GADD45A
09:30–10:00 **Bryan Cullen**, Duke University, Durham, NC
Viruses and MicroRNAs
10:00–10:30 **Thomas Stamminger**, Institute for Virology, Universität Erlangen-Nürnberg
Viral Silencing Mediated by Components of PML Nuclear Bodies
10:00–10:30 Break
11:00–11:30 **Janos Minarovits**, University of Szeged
Epigenetics of EBV-Host Cell Interactions
11:30–12:00 **Michiel Vermeulen**, Radboud Institute, Nijmegen
Quantitative Interaction Proteomics for Epigenetics
12:00–12:30 **Armin Ensser**, Institute for Virology, Universität Erlangen-Nürnberg
Rhadinovirus Epigenetics and Cellular Restriction
12:30–14:00 Lunch Break

Session VI: Regulation

Chair Christoph Plass, Heidelberg

14:00–14:30 **Dirk Eick**, Helmholtz Zentrum, München
The RNA Polymerase II Carboxy-terminal Domain (CTD) Code
14:30–15:00 **Heinrich Leonhardt**, LMU, München
Role and Regulation of DNA Modifications in Development and Disease

15:00–15:30	**Michal R. Schweiger**, Center for Genomics, Cologne University *The Bromodomain Protein BRD4 – a Mediator between Oxidative Stress and Epigenetics*
15:30–16:00	Break
16:00–16:30	**Boris F. Vanyushin**, Belozersky Institut, MGU, Moscow *Short Biologically Active Peptides as Epigenetic Modulators of Gene Activity*
16:30–17:00	**Stefan Ameres**, Institute for Molecular Biotechnology, Wien *Mechanism and Biology of RNA Silencing*
17:30	**Farewell—End of Symposium:** Walter Doerfler