# Epigenetics and Human Health

Sophie Rousseaux • Saadi Khochbin
Editors

# Epigenetics and Human Reproduction

Springer

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# Preface to the Series

"Epigenetics and Human Reproduction" is the first volume of a new Springer book series on epigenetics and human health and covers various aspects of human reproduction in relation to epigenetic reprogramming during female and male gametogenesis.

Drs. Saadi Khochbin and Sophie Rousseaux, the volume Editors of "Epigenetics and Human Reproduction", are specialists in this biomedical field. They both direct research programmes at the Albert Bonniot Institute in Grenoble (France), one of the centres in the epigenetics of reproduction in Europe. Combined, their expertise goes from fundamental studies using cells and animal models to the understanding and clinical follow-up of infertility in humans. This broad understanding of chromatin and epigenetics in reproduction was most beneficial to the balanced choice of the 15 chapters, each of which covers a different aspect of this emerging field. In fact, this comprehensively referenced book is the first one of its kind. It will be of considerable interest not only to clinicians and biomedical researchers but also to advanced medical and biology students.

Many different themes are presented in the book, which is introduced by Professor Bernard Jégou (Rennes, France) in the following pages. On the clinical side, chapters cover disorders and cancers linked to with human reproduction that are of epigenetic origin and discuss potential consequences of assisted reproduction procedures, in vitro manipulation, and somatic cell nuclear transfer technologies. This is nicely complemented with several chapters on the nuclear organisation and quality of human sperm and the epigenome of the preimplantation embryo. A major, more fundamental part of the book concerns epigenetic transitions and transcriptional regulation (including small RNAs) in developing germ cells. As concerns spermatogenesis, the highly specific chromatin remodelling process of spermiogenesis is being highlighted, also in the context of its possible consequences for the next generation. The ultimate aim of germ cell development in mammals is to produce haploid gametes, a process that requires meiosis to occur. This unique cell cycle is presented with a specific emphasis on the role of chromatin modifications. For instance, meiotic recombination, the complex crossing-over mechanism that provides the genetic diversity between the gametes, is now known to involve specific histone modifications and histone variants.

This then is the first volume of the new Springer Series "Epigenetics and Human Health", edited by Professor Jörn Walter (of the University of Saarbrücken, Germany) and myself, together with Dr. Mario Noyer-Weidner (Berlin, Germany). During the last years, Springer has become much interested in the novel discipline of Epigenetics, which has so many emerging links with human health. We are very pleased to having been involved in this exciting enterprise. Several other volumes are currently being prepared by invited Editors, to be published during the coming year, including a volume on "Epigenetics and Psychiatry" and one on "Environmental and Nutritional Epigenetics", two other important emerging themes in medical research. It is now timely to bring together these new epigenetic discoveries of relevance to human disease and to present them in broader contexts with comprehensive referencing of the existing literature. This is the overall aim of our book series, so that it will be of lasting interest to medical and scientific readers. We hope you will enjoy this volume on human reproduction and will find it useful for your professional endeavours.

September 2010

Robert Feil
Mario Noyer-Weidner
Jörn Walter

# Foreword

I am pleased and honored to have been invited to write the introduction to this volume depicting the state of the art of "Epigenetics and Human Reproduction". As I have no particular credentials in epigenetics as such, I would guess that it is by virtue of me having been an observer and sometimes a participant in the progress in the field of reproduction over the past 30 years that I am humbly entitled to comment on the impressive work produced by the numerous contributors to this volume.

For a long time, the sequencing of entire mammalian genomes, including that of humans, appeared impossible. This is probably why, when the Human Genome Project was rendered feasible by the technological revolution in the field of molecular biology in the 1980s and was officially launched in 1990, the expectations were enormous. By part of the scientific community, and then the public opinion, it was believed that mapping the whole human genome and sequencing its DNA would by itself reveal how species differ and even what makes each human being unique. However, when the human genome was finally sequenced in 2001, together with that of other selected species (e.g., the mouse in 2002), it became clear that genome sequences are so similar that they cannot per se account for the great diversity within and between species. Similarly, the illusion that for every disease genetic components could reveal its causes (and thus be used for its prevention or cure) sadly faded.

Thus, by the beginning of this century, it had become clear that the extraordinary complexity of genetic regulation relies in part on changes in gene expression, without alterations in the DNA sequence itself, that is, on *epigenetics*. The consequence of this conclusion is that the number of publications in this field has expanded exponentially, as has the number of scientists working at one level or another in epigenetics. To the most enthusiastic analysts of the evolution of our knowledge about the regulation of genes, the epigenetic revolution is the equivalent in biology of the revolution in our understanding of the universe induced by the emergence of the new physics at the beginning of the twentieth century. Epigenetics and epigeneomics have become such strategic issues that, exactly 20 years after the start of the Human Genome Project, an International Human Epigenome Consortium (IHEC) was launched in Paris in March 2010. Its goal is to map 4,000 reference epigenomes within the next 10 years.

But how has the epigenetic revolution affected the research aimed at improving our understanding of reproduction in mammals? Most interestingly, from the beginning, the words "epigenetics" and "reproduction" have been consubstantial. Indeed, it was from cloning experiments with the mouse embryo in the 1980s that one of the primordial phenomena of epigenetics was discovered, that is, *genomic imprinting*. This phenomenon enables the embryo to distinguish between the maternal and paternal alleles it inherited. As a consequence, in the mammalian germ cells, the mother and the father contribute different epigenetic patterns for specific genomic *loci*. This finding contradicts a basic tenet of Mendelian genetics that the alleles from the father and from the mother are functionally equivalent. Understanding this phenomenon rapidly proved crucial to our comprehension of the origin of several human disorders, including the Angelman, Prader–Willi, and Beckwith–Wiedemann syndromes, which all result from abnormal imprinting patterns. It also raises the question of whether manipulation of gametes, such as that occurring during assisted reproduction, might induce epigenetic disruption of a chromosomal region (i.e., epimutations), an issue of great importance in humans as well as in animal models (Chaps 1 and 4). A better understanding of this problem will help greatly in evaluating the risks of artificial reproductive technologies (ART) to the *conceptus* and, we can hope, will increase its safety.

Comprehending the etiology of infertility, which currently affects about 10–15% of the individuals in the general adult population in the developed world requires that we understand how the chemical modifications of DNA and its associated proteins via DNA methylation, histone modification, and small noncoding RNA regulation influence gene expression in both the male and the female germ lines and lead to normal embryo development (Chaps 3, 6–9, 11–15). Equally important, the outcome of epigenetic research is likely to improve our knowledge of the causes of testicular cancer, the incidence of which is increasing worldwide (Chap. 2). Furthermore, deciphering the pathways by which epigenetic modifications within the primordial germ cell control the restoration of cellular totipotency also appears crucial and will affect our perception of how the roughly 250 different types of tissues are generated in individual mammals and maintained during development (Chap. 5).

Last but not the least, coping with the fast development of the technologies required to study epigenetics, and the enormous amount of data produced by the IHEC program represents a real challenge for the community of "repro-epigeneticists" (Chap. 10).

There is no doubt that the field of reproduction will benefit from the ongoing international research effort in epigenetics. Conversely, because the germ lineage is at the origin of life and because the cellular and molecular mechanisms that underlie the germ line are particularly complex, progress in understanding the fundamental substrate of fertility and infertility will no doubt have far-reaching consequences in numerous different domains, including systemic diseases such as cancers.

Beyond the scope of this volume is another aspect that deserves to be highlighted in this introduction, related to what is now known as *"transgenerational inheritance"*. The question here is to understand how environmental influences

such as nutrition and chemical agents (solvents, metals, particles of different kinds, solvents, endocrine disruptors...) can alter the germ cell epigenome to make the transmission of epigenetic phenotypes possible. Although marked by a certain degree of controversy, as is normal for any emerging scientific field, an ever increasing number of animal studies progressively sustain that this phenomenon is real. The findings are strengthened by studies in human populations, showing that malnutrition during pregnancy may permanently alter chromatin at fetal stages such that epigenomic changes induced in the germ line are passed on to offspring and be at the origin of diseases such as diabetes and cancer.

In conclusion, this volume provides a highly up-to-date source of information that should prove exceedingly useful to researchers, teachers, and students in human and animal reproduction, as well as to clinicians concerned with ART and with human fertility issues in general. We hope that the launching of the IHEC will also help to focus attention on the crucial importance of developing the field of "epigenetics and reproduction" and that it will contribute to convincing both IHEC and funding agencies and institutions worldwide to allocate more funds to this fundamentally important field of research.

Rennes, France Bernard Jégou
July 2010

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