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## Preface

While timorous knowledge stands considering, audacious ignorance hath done the deed.

-Samuel Daniel

Genomic imprinting has been fascinating us for over three decades and has provided many emerging scientists with the chance to hit their stride in a frontier posing many unexpected questions and even more surprising answers. Imprinting is the process by which the non-equivalence of the paternal and maternal genomes is established, leading to parent-of-origin-specific effects. The most ostensible effects in mammals of parental-specific marks—and to date, the most accessible to study—are the differential outcomes in gene expression between the paternal and maternal alleles. During the first two decades, the field grew hand in hand with technological innovations in embryology and gene targeting, mainly in the mouse. In fact, advances in imprinting and other unique regulatory mechanisms were instrumental in establishing Epigenetics as the “umbrella organization,” as Davor Solter so wittily calls it (1). Many of the broader principles of epigenetic regulation were unearthed by studying imprinted domains (2) and their alterations in cancer and developmental diseases. As technology has moved forward into the “genome-wide” and “high-throughput” arenas, many imprinted regions have been even more fully characterized—with an abundance of information on the epigenetic modifications occurring at specific domains and throughout development. The availability of genome sequences and their variations have moved the field forward enormously. We now know that imprinted genes tend to occur in clusters, that the mechanisms by which the inactive genes are silenced vary from one region to another, that establishment and erasure of the imprints occur at different developmental stages for male and female germ cells, and that DNA methylation is the most consistent candidate for the imprint, at least in the embryo. Clusters of imprinted genes are regulated in *cis* by long-range control elements, designated as imprinting control regions, and these are the sequences bearing the memory of parental origin. Moreover, noncoding RNAs with regulatory roles are present in all imprinted domains.

It is interesting to note, however, that we have yet to answer some of the fundamental questions that the discovery of imprinting posed when it was first described—i.e., how widespread is imprinting across the animal and plant kingdoms, how does the imprinting process vary across genotypes and species, how is the imprint targeted to specific DNA sequences, how is the marking erased, what is the mechanism of tissue-specific and stage-specific imprinting (3), and what is the functional role and origin of imprinting (4). The huge amounts of genome-wide epigenetic data are correlative and have not provided an answer to the question of whether the marks are the cause or consequence of gene expression state, nor have we gained insight into how chromatin-modifying enzymes are targeted to specific sequences. Still to be achieved is the feat of conferring imprinting on a normal gene by transferring a specific sequence into its vicinity. A host of candidate imprinted genes await validation by site-specific molecular studies. Taking advantage of the combined

genomic and epigenomic data, we now need more detailed mechanistic models to be tested. In addition, new questions have emerged on the variability of imprinting marks in the population, the effects of culture and in vitro fertilization on imprints, the nature of imprinting in extraembryonic tissues, and the role of noncoding RNAs, among others.

*Genomic Imprinting: Methods and Protocols* is a survey of the technologies that are being applied to advance the study of imprinting. It includes new technologies that are accelerating the pace of discovery of imprinted genes and characterization of their epigenetic profile, bioinformatic procedures for prediction and comparative analyses of imprinted genes, as well as methods in embryology and basic molecular biology that have been employed for many years, some appearing in new versions for small cell numbers. Undoubtedly, focusing on individual imprinting clusters has uncovered many novel mechanisms in gene regulation, and doing so with traditional but ever more sensitive molecular biology tools will continue to be essential in elucidating the molecular logic of imprint establishment and erasure.

Since many of the compelling questions of the field will require querying very small numbers of cells, we anticipate that the newer technologies will eventually be scaled down to meet this requirement. Also, bioinformatics will continue to expand its influence in the field to bring new insights into the evolutionary history of imprinting. Hopefully, we will also begin to see more of an impact of our imprinting research on other parent-of-origin effects (5). Although attempts are continuously being made to synthesize and generalize our knowledge of imprinted genes, the fact remains that each imprinted domain is unique in some respects, and there is still much to be explored at the molecular level. There is no doubt the next few years will unveil both much-awaited answers and new questions to keep us busy for many exciting years to come.

I thank all the authors for their outstanding contributions to this volume.

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