# Preface

Genetic recombination and recombinational DNA repair are two facets of a universal process that is essential for genomic integrity. This process, termed homologous recombination, occurs when a broken or damaged chromosome uses a second, homologous chromosome as a template for its repair. In meiotic cells, double-stranded DNA breaks are programmed, and the ensuing recombination serves to link homologous chromosomes via crossovers to ensure their proper segregation during the first meiotic division. In mitotic cells, recombination is used to repair accidental DNA damage, typically engaging the sister chromatid as the repair template and minimizing crossover formation in order to maintain chromosome stability. Recombination is an elaborately orchestrated process involving dozens of proteins and strict regulation to avoid interference with other DNA metabolic processes, the formation of potentially toxic intermediates, and the generation of chromosomal rearrangements.

The first part of this volume (Mechanisms of Recombination) provides a lucid overview of the sophisticated mechanistic understanding of homologous recombination that has accumulated over the past decades. Significant portions of the overall recombination process have been reconstituted in vitro using an impressive list of purified proteins from bacteriophages, *Escherichia coli*, *Saccharomyces cerevisiae,* and humans. These efforts not only have provided detailed mechanistic and, at times, structural insights into the underlying processes but have also led to the identification of a growing cohort of proteins that impinge on the core recombination machinery. Importantly, the development of sensitive assays enables quantitative analysis of variants in human recombinational DNA repair in order to assess their functional significance to leverage the deluge of human cancer genome sequencing data.

The second part (Regulation of Recombination and Genomic Maintenance) places homologous recombination into the broader context of the ensemble of cellular processes affecting the DNA substrate. Regulation is required to coordinate recombination with alternative DNA repair processes and DNA damage tolerance pathways, transcription, and replication. Specialized chromosomal domains (centromeres and telomeres) pose additional challenges to recombination. Moreover, the chromosome substrate for recombination has a dynamic chromatin structure, modulated by a myriad of posttranslational modifications, remodeling, localized compaction (euchromatin vs. heterochromatin), and cell-cycle-specific condensation during chromosome segregation. Although the contribution of sister chromatid cohesion to template choice in recombination has been evident for some time, we only recently learned about the dynamics of the nuclear territories that chromosomes occupy after the induction of DNA damage. The coordination of recombination with other nuclear processes and a dynamic nuclear architecture requires regulatory processes that we are only beginning to fathom. Furthermore, the homologous recombination pathway itself requires regulation, which can be imparted through modification of the chromosomal DNA or the protein factors involved. Both areas have seen an explosion of reported posttranslational modifications, whose significance still largely needs to be established. An important aspect of quality control in recombinational DNA repair and regulation of recombination outcome is pathway reversibility, providing a clever engineering solution to impart robustness and regulation with surprising genetic implications. Finally, the selective advantage resulting from these regulatory networks is to maintain genomic stability between generations and during ontogenesis in order to calibrate mutation rates and avoid genomic rearrangements. There are evident consequences for the etiology and therapy of human diseases, specifically cancer but likely also additional disorders.

The chapters constituting the third part of this volume (Meiotic Recombination) retrace the historic origin of the study of homologous recombination in eukaryotes, which focused on meiotic recombination and its impact on genetic diversity. These early studies revealed the essential role of crossing-over in meiotic chromosome segregation and established the fundamental features and pathways that underpin present-day models of recombination. Studies of meiotic recombination have also contributed much to our understanding of the specific DNA intermediates involved. Contemporary investigations frame the DNA steps of meiotic recombination in the larger context of the meiotic program, which serves to connect and assort homologous chromosomes with unfailing accuracy to produce euploid gametes. The fundamental differences between meiotic recombination and recombinational repair in somatic cells are highlighted for each step of the process. These distinctions define the elaborate meiosis-specific processes that repurpose recombination to effect homolog pairing and crossing-over. A recurring feature is feedback regulation between the DNA events of recombination and the morphogenesis of meiotic chromosomes (pairing and synapsis), which occurs through physical coupling and functional interdependence of these processes. The role of defective recombination in meiotic aneuploidy has been known for some decades, but the impact of genes affecting core recombination functions, regulatory processes, and chromosome structure on human fertility is only now starting to emerge.

If this short summary has whetted your intellectual appetite, then you will enjoy our elaborations on these topics and appreciate even more the in-depth chapters by recognized leaders in the field, who have helped shape the discussion of these topics over the last decades.

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