

Preface

In 1942, Julian Huxley referred to the cross-disciplinary, unified evolutionary theory as the *modern evolutionary synthesis*. In the early part of the twentieth century, Fisher, Haldane, and Wright—and later Mayr, Dobzhansky, and others—produced a revised model of Darwinian evolution that rationalizes Mendelian genetics in the context of natural selection. The presence of pre-existing heritable variation is key for selection to be effective and is a contingency of adaptability. At the same time, mutation is proposed to accumulate at a constant rate, regardless of selective pressures and environmental cues.

The discoveries of epigenetic inheritance and stress-induced mutation have challenged the claim of independence between mutation and selection processes. The ability of an organism to undergo genetic or epigenetic change in response to environmental stresses suggests an ability to alter the *rate* of mutation, which could take effect globally or at specific parts of the genome, and temporarily or permanently. Mutation rates can be altered globally and permanently by the presence of mutator alleles, temporarily due to transient events such as environmental stress, or locally at “hotspot” locations in the genome. Such mechanisms are clearly valuable from an evolutionary perspective, as it is advantageous for mutation to be restricted in both time and space, if most selectable mutations produce deleterious outcomes.

This volume compiles key evidence for stress-induced genetic and epigenetic mutation, integrating cross-disciplinary observations from a number of species and biological systems, including human. The observations have vast implications for evolutionary biology but also for human medicine. For example, genomic instability is now recognized as a hallmark of most cancers. Tumor resistance and recurrence are modeled within the context of clonal expansions. The comprehensive understanding of stress-induced mutagenesis and the processes underlying evolvability, studied across many biological systems, will enable gains in the treatment and management of cancer, as well as other human disorders that result from damaged or unstable genomes.

Stress-induced mutagenesis has been most widely studied in bacterial systems. In the first chapter, Ivan Matic describes the role (and regulation) of mutator alleles

and stress-induced mutagenesis pathways in the evolution of bacterial populations. The chapter by Susan Rosenberg and colleagues dissects the pathways to stress-induced mutagenesis, focusing specifically on the localization of mutagenic repair to double-strand breaks. This chapter provides some exciting new evidence that argues mutagenesis is not an inevitable consequence of DNA repair. This has been a long-standing point of debate. In his classic critic, "Adaptation and Natural Selection," George Williams argued that mutation rate is a "mechanical inevitability," the byproduct of physical limitations in the fidelity of DNA repair processes and not the product of natural selection. Rosenberg and colleagues now show that stress-induced mutagenic repair is activated by repair components that are not required for the proper resolution of a DNA break. They also discuss the localization of mutation, during stress, to DNA breaks, which minimizes the impact of deleterious mutations to the genome. In the third chapter, Eduardo Robleto and Ronald Yasbin describe transcription-coupled mutagenesis pathways that illustrate another way in which mutagenesis can be triggered temporally by environmental cues, and then localized to focused portions of the genome. In the fourth chapter, Milton Saier and colleagues present intriguing evidence that stress can activate transposons, which play roles in gene regulation and disease.

From the seminal work of Lindquist and Rutherford, the stress-activated Hsp90 chaperone is now known to participate in the canalization of traits, something first described by Conrad Waddington more than a half-century ago. Hsp90 normally functions to buffer client proteins against the effects of genetic variation. Severe environmental stress can overwhelm the chaperone's buffering capacity, causing previously cryptic genetic variation to be expressed. In Chap. 5, Douglas Ruden and colleagues share very exciting evidence that, in flies, Hsp90 can induce novel epigenetic changes in addition to exposing existing variation. Shunsuke Ishii and colleagues continue the discussion of epigenetics in a very compelling chapter that maps a molecular pathway by which the ATF-2 family of transcription factors facilitates the inheritance of stress-induced epigenetic changes.

As mentioned above, focusing mutagenesis in time and space minimizes the impact of deleterious mutations across the genome. Tandem repeats are an important source of functional variation that also fit these constraints. Tandem repeat mutation rate is modulated by global and local factors and triggered by temporal events such as stress. Many tandem repeats affect morphological, behavioral, and life-history traits through subtle and quantitative effects on gene function. Most interestingly, the incremental functional impact of repeat mutation even further decreases the frequency of catastrophically deleterious effects. In Chap. 7, John Wilson and colleagues outline key lines of evidence in human cells that reveal how repeat mutation is modulated by local and global factors, as well as stress, transcription, and DNA methylation.

In Chap. 8, Peter Glazer and colleagues outline the mechanistic details by which the genomes of human cells become unstable as a result of exposure to hypoxia, or oxygen deprivation. This is a particularly important stressor in the context of cancer, as developing tumors experience hypoxic stress prior to the recruitment of dedicated blood supplies through angiogenesis. The finding that hypoxia and other stres-

sors can destabilize cancer genomes is very significant, as it is likely that tumors draw upon this variation to adapt to their microenvironments and to resist drug treatment. In the following chapter, Jac Nickoloff and colleagues describe a mechanism for the fascinating and equally frightening observation that in human cells, delayed transgenerational genomic instability can be induced by low-dose radiation treatment. The possibility that radiotherapy can be a trigger for future cancer development raises important questions about the safety and appropriateness of such a therapy. In the related and following chapter, Carmel Mothersill and colleagues explore stress-induced bystander effects and highlight the relevance of this phenomenon for cancer and adaptive evolution. Denise Montell and colleagues present in Chap. 11 some rather surprising studies that document the reversal of the apoptotic process. They present evidence that dying cells with damaged genomes can revert to living and proliferating cells, in a process they cleverly term *anastasis*. One implication of this phenomenon is that it could be a possible mechanism for tumor cells to survive and even resist treatment. In Chap. 12, Yuri Dubrova documents provocative evidence, in rodents, for transgenerational instability induced by radiation or chemical toxins. The findings are particularly compelling as the genomic instability increases in subsequent generations. The emerging evidence for this phenomenon in humans is frightening, particularly in the context of the recent Fukushima Daiichi nuclear disaster in Japan.

The final chapter by Subhajyoti De summarizes the emerging revolution in high-throughput sequencing. The affordability and availability of high-throughput sequencing has created an unprecedented surge in the use of genomic data in basic, translational, and clinical research. The ability to rapidly sequence and analyze entire genomes or populations of genomes is transforming the study of mutagenesis and genome evolution. For the first time, rather than utilizing engineered assays or genomic markers, the complete and unbiased spectrum of stress-induced changes can be directly measured genome-wide. The implications for cancer are vast as well, since tumor sequencing now enables the identification of trigger mutations and as well as passenger mutations that could serve as targets for tumor susceptibilities.

I am so grateful to the chapter authors for their enthusiasm and for helping me assemble this volume. As a graduate student, “DNA Repair and Mutagenesis” was my bible. The textbook, helmed by Errol Friedberg, is one of the most complete resources for understanding the intricacies of DNA repair and genome stability. In preparing this volume I strived to produce a worthy and complementary resource documenting the evidence for stress-induced genetic and epigenetic mutation across all biological systems; and the implications of these processes to evolutionary theory and cancer genetics. The authors of these chapters are leaders in their respective disciplines, and I am incredibly thrilled and grateful that so many of them were able to collaboratively assemble what I think is one of the most comprehensive cross-disciplinary resources for this exciting and relevant field.

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