
Preface

Intracellular checkpoint controls constitute a network of signal transduction pathways that protect cells from external stresses and internal errors. External stresses can be generated by the continuous assault of DNA-damaging agents, such as environmental mutagens, ultraviolet (UV) light, ionizing radiation, or the reactive oxygen species that can arise during normal cellular metabolism. In response to any of these assaults on the integrity of the genome, the activation of the network of checkpoint control pathways can lead to diverse cellular responses, such as cell cycle arrest, DNA repair, or elimination of the cell by cell death (apoptosis) if the damage cannot be repaired. Moreover, internal errors can occur during the highly orchestrated replication of the cellular genome and its distribution into daughter cells. Here, the temporal order of these cell cycle events must be strictly enforced—for example, to ensure that DNA replication is complete and occurs only once before cell division, or to monitor mitotic spindle assembly, and to prevent exit from mitosis until chromosome segregation has been completed. Thus, well functioning checkpoint mechanisms are central to the maintenance of genomic integrity and the basic viability of cells and, therefore, are essential for proper development and survival.

The importance of proper functioning of checkpoints becomes plainly obvious under conditions in which this control network malfunctions and fails. Depending on the severity and timing, failure of this machinery can lead to embryonic lethality, genetic diseases, and cancer. Cancer in particular has been recognized as a disease in which acquired mutations and loss of genomic integrity decidedly contribute to its origination and progression. Most, if not all, cancer cells exhibit incomplete or malfunctioning checkpoint control pathways, which constitutes a situation that is further aggravated because this absence of efficient controls allows for even more deleterious mutations to accumulate. The enhanced potential of cancer cells to survive under suboptimal conditions and their increasing ability to withstand chemotherapeutic intervention are but two of the consequences. Thus, identifying the molecular components of checkpoint controls and understanding the complexity of their spatiotemporal interactions is a major goal of current cancer research. Besides satisfying our academic curiosity, novel insights and advances in this complex area are essential for the development of new and more effective therapies.

Experts from 10 different countries have contributed their detailed knowledge to the present two-volume work, *Checkpoint Controls and Cancer*, which

presents a collection of indispensable tools and their applications that will further advance our understanding of the intricacies of checkpoint controls. Each volume is divided into two parts. Part I of *Volume 1: Reviews and Model Systems* contains comprehensive review articles that introduce all of the important components of checkpoint controls, describe their intricate interactions, and highlight the relevance of these processes to the cancer problem. Here, the amazing complexities of checkpoint controls—and the gaps that exist in our knowledge thereof—become distinctly apparent. Part II illustrates the advantages of utilizing diverse model systems, such as intact human skin or knockout mice, as well as other most useful organisms, such as *Xenopus*, *Drosophila*, *Caenorhabditis*, and yeast. As has been shown time and again, the convergence of information from various model systems is able to crossfertilize and accelerate research both across disciplines and beyond the boundaries of a particular species. This is especially true for the study of yeast, which has already provided major insights into the function of cell cycle and checkpoint controls. *Volume 2: Activation and Regulation Protocols* is a collection of “how-to” chapters with stepwise instructions that focuses on the individual components of checkpoint controls and describes the detailed analysis of their activity. Part II completes this collection by providing various experimental approaches for the manipulation of checkpoint pathways and the analysis of the resulting consequences for the cellular phenotype. Altogether, this collection of protocols and proven techniques will be useful for all researchers, whether they be novices who need step-by-step instructions, or experienced scientists who want to explore new approaches or model systems for the study of checkpoint controls and cancer.

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Axel H. Schönthal