

# Preface

Colorectal cancer (CRC) represents a major healthcare burden worldwide for two simple reasons: it is common and it is deadly. And while improvements in early detection have helped to reduce the incidence of CRC-related death over the past several decades, the overall frequency of the disease is likely to increase steadily due to its connection to western style diet, which is spreading across the globe, and to obesity and chronic inflammation (i.e., inflammatory bowel disease), which are also rapidly increasing in incidence. As a result, a new generation of effective CRC therapies is greatly needed. The search for new therapies to treat CRC is intertwined with the identification of the molecular etiology of the disease.

Even prior to the advent of whole genome sequencing, many of the mutant genes that contribute to CRC (*APC*, *KRAS*, *TP53*) were known from targeted sequencing efforts. As a result, CRC has become the paradigm for multistage tumorigenesis, where the histologically defined transition states from normal tissue to malignancy can be associated with mutations in specific genes or pathways. As we enter the post-genomic era, it is possible that most, if not all, of the genes that contribute to CRC in a meaningful way have been identified. Now it is time to leverage the extensive mutational information to establish new therapeutic strategies. This will require a combination of functional genomics (i.e., genetics), medicinal chemistry, and pre-clinical and clinical efforts.

The goal of this book is to provide a broad overview of the state of understanding of the molecular pathogenesis of CRC. This book is organized as a timeline of the study of CRC. Chapters 1 and 2 provide a general and historical viewpoint of the role for genetic changes and genomic instability in CRC. Chapters 3–8 discuss the roles of specific pathways (RAS, PI3K, TGF- $\beta$ ) or environmental conditions (inflammation). And Chaps. 9–12 look toward the future, focusing on the potential for genome-wide analyses to find new genes/pathways that contribute to CRC. I hope that the reader will get an appreciation for the rich history of CRC research and a fresh perspective on the possibilities for emerging therapeutic options.

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