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GENETIC MECHANISMS IN MULTIPLE ENDOCRINE NEOPLASIA TYPE 2

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CONTENTS

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PREFACE

From a variety of scientific perspectives, the multiple endocrine neoplasia, type 2 (MEN 2) syndromes provide a setting for the study of a fascinating array of important biological questions. In turn, our understanding of basic biological processes, such as signal transduction and development, has rapidly augmented our insight into the biological behavior of the cancers of MEN 2. Finally, activating mutations in the ret tyrosine kinase gene have been shown to underlie MEN 2. These mutations represent the first demonstration of an activating mutation in an oncogene in a hereditary cancer syndrome; this finding has served to focus our attention regarding the specific molecular mechanisms of tumor development in MEN 2.

In order to understand the biology of MEN 2 syndromes, it is necessary to take an integrated approach. Mutations and alterations in gene expression and signal transduction must be placed in context of their effects on the biology of the thyroid C-cells and adrenal chromaffin cells which are the progenitors of medullary thyroid carcinoma and pheochromocytoma. This will require an understanding of the developmental, cell and molecular biology of these cells, as well as an understanding of the function of normal or mutated ret proteins. This book is a first attempt to bring together these topics. In chapter 1, Ball discusses the clinical aspects of MEN 2, including the impact on clinical management of MEN 2. In chapter 2, Ponder and Pierotti address the spectrum of ret mutations in MEN 2, and their implications for tumorigenesis. In chapter 3, Fusco et al examine the signal transduction pathways which may be affected by ret activation. In chapter 4, Myers et al review the signal transduction pathways which control differentiation in the well-characterized pheochromocytoma cell line, PC12. Chapters 5 and 6 discuss the normal and abnormal development of adrenal chromaffin cells from the neural crest. Vogel (chapter 5) details the normal migration of neural crest cells to the adrenal medulla, their commitment to the sympathoadrenal lineage and their differentiation into neuronal or chromaffin cells. Tischler and DeLellis (chapter 6) examine how, in MEN 2 and in rodent models of pheochromocytoma, the adrenal medulla undergoes hyperplasia, culminating in tumor development. Russo and Lanigan (chapter 7) review the neuronal properties of C-cells, and discuss possible effects on this differentiation during MTC tumorigenesis. Nelkin (chapter 8) and Moley (chapter 9) discuss possible steps in tumor progression in MTC and pheochromocytoma.

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