Endocrine Tumor Syndromes and Their Genetics

Volume Editor

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Foreword

With the sequencing of the human genome in 2000, it was anticipated that most human disease would come into focus and that our increased understanding of molecular biology would initiate a whole range of new effective therapies. That this has not, for the most part, come about has led to a reconsideration as to the relevance of DNA technology to modern medicine. It is evident that the task of comprehending and treating human disease remains complex and difficult. However, there is one area in which our increased molecular knowledge has led to a considerable increase in our understanding of disease, and that is in endocrine oncology. We now realize that many ‘sporadic’ endocrine tumours arise on a background of germline mutations, even in the apparent absence of other syndromic features. This is particularly the case for phaeochromocytomas and paragangliomas, where as many as 30% of patients presenting with these tumours may have a ‘genetic syndrome’. These are exciting times, and I am delighted that Constantine Stratakis has undertaken to review the current ‘state of the art’. As a major contributor to this area, he has been able to bring together a stellar group of contributors to summarise our current knowledge. While the impact of our understanding of these germline syndromes on somatic tumour aberrations is less than might have been anticipated, these new findings have provided insights into novel signalling pathways which cannot but enhance our understanding of tumorigenesis in general.

From a personal point of view, I am really happy to have initiated this volume, which is the last in the series where I have been Editor-in-Chief. It has been a real pleasure having the freedom to choose the most engaging and fast-moving areas of modern endocrinology for the ‘Frontiers’ series, and I sincerely thank my talented clinical and scientific volume editors over the years who have made this series so successful. I am also very grateful to Thomas Nold (Karger Publishers) who has assisted me over much of this time, and has frequently but gently prodded me in the right direction in the most diplomatic manner. I am delighted that Prof. Ezio Ghigo is to take over the series, and I leave in his safe and experienced hands a series which I am sure will continue to flourish.

Ashley B. Grossman, Oxford
Preface

What Is New in the Genetics of Endocrine Tumors? From Classic Multiple Neoplasia Syndromes to Various Germline or Somatic Mutations in Sporadic Tumors

Contemporary genome-sequencing studies indicate that each human carries as many as 100 loss-of-function mutations with more than 20 genes completely inactivated [1]. In a recent Editorial, I stated that ‘a patient can have as many genetic variants as he damn pleases’ [2]. Hence, the subtitle of this note, which serves as an introduction to a wonderful collection of articles, written by leaders in the field, as updates on the genetics of endocrine tumors: ‘From classic multiple neoplasia syndromes to various germline or somatic mutations in sporadic tumors’. The order of the reports in the book follows the theme of the subtitle [3–13] that is also the theme of this introductory note.

In other words, the description of the classic multiple endocrine neoplasia (MEN) syndromes, MEN1, MEN2, von Hippel-Lindau disease (VHLD) and Carney complex (CNC) [3–6], and their molecular elucidation led to the description of new associations: MEN 4, the paraganglioma syndromes, and Carney triad, the newest form of MEN to be described [7–9]. The description of these latter associations became possible after the germline genetic defects were identified in the former, because it became clear that a number of patients with pituitary tumors, pheochromocytomas, paragangliomas and other adrenal tumors did not have MEN1, MEN2, VHLD or CNC. In turn, the newly described associations allowed for the investigation of cohorts of patients with sporadic or inherited endocrine tumors, many of them with mutations in genes that were not previously suspected to be involved in endocrine tumors, such as, for example, the gene coding for the aryl hydrocarbon receptor interacting protein or AIP or cyclin-dependent kinases and their inhibitors. Today, a number of previously thought sporadic endocrine tumors are found to be predisposed to germline defects, some of these being simple genetic variants that do not always cause disease. This is well described in the chapters on pituitary, thyroid and parathyroid tumors in this book [10–12]. Finally, the careful investigations of cohorts of patients with genetic conditions that we knew them to be at the periphery of endocrinology, such as Peutz-Jeghers syndrome, neurofibromatosis or tuberous sclerosis, led
to the description of a variety of endocrine tumors [13] and pointed to the respective molecular pathways and their potential involvement in endocrine tumorigenesis.

A book cannot capture everything that is going on in a field and, in our days, it is quickly relatively outdated. But a book like this should aspire to reflect the theme of the moment, represent the most significant advances of the field at present, and provide a useful compendium for at least the near future. I do believe the chapters in these series reflect well the changing world of modern genetics in endocrine tumors and its impact on clinical practice beyond the obvious implications for our understanding of endocrine tumor formation, molecular biology of cancer, in general, and the potential therapeutic implications.

It is indeed a new world out there for the practicing clinician. Every time we see a patient with the admittedly rare endocrine tumor, we now have to think somewhat differently from the past. We have to be knowledgeable about the associations described in this book (and suspicious of many new ones that have yet to be described) and be able to incorporate systems biology information into our daily clinical practice. When I proposed paraphrasing Hickam’s dictum, ‘a patient can have as many genetic variants as he damn pleases’, I did not say that all sequence defects that are identified today by modern sequencing methods cause various diseases; the truth is far more complicated [2]. The evidence is that there is some redundancy, safety loops, and a tremendously complex molecular balance in human biology. But variants are there, in our genomes, and they do influence biology and how we respond to the environment; clinicians have to incorporate modern genetics in their daily practice. Likewise, educators and researchers have to introduce molecular pathways and their genetic variability in their teachings and understanding, respectively, of classic physiology and pathophysiology.

I thank Karger Publishers for asking me to edit this book; all staff members were wonderful to work with. A huge thank you goes to all our authors who provided timely their work product; our audience, I hope, will agree with me on the outstanding quality of all submissions. Finally, there was no research funding that was used for this editorial text and the opinions and statements made above are not those of the agencies or other organizations that have funded my official duties as a National Institutes of Health Senior Investigator.

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