EDITORIAL

65 YEARS OF THE DOUBLE HELIX

It’s all in the DNA: understanding and managing endocrine neoplasms

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This paper is part of a thematic review section celebrating 65 Years of the Double Helix. The guest editors for this section were Charis Eng, William Foulkes and Jérôme Bertherat.

“Science is beautiful when it makes simple explanations of phenomena or connections between different observations. Examples include the double helix in biology and the fundamental equations of physics.”

– Stephen Hawking

Sixty-five years ago, a short letter was published in Nature, the closing sentences of which include the justly famous phrase “It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.” Crick wasn’t a typical scientist and Watson isn’t an Englishman, but this typical “English understatement” has become one of the most widely known phrases among scientists, along with “Eureka” and “Dans les champs de l’observation, le hasard ne favorise que les esprits préparés” (or at least in its English translation “In the fields of observation, chance favours only the prepared mind”). Why has this phrase become famous? Not only because the prediction turned out to be correct, or for its laconic pithiness, but also because genomic medicine led directly from that phrase, and genomic medicine is now the most active area of both clinical practice and research in medicine. In the broadest sense, genomic medicine uses genomics (omics) to personalize healthcare by risk stratifying and managing.

This special issue of Endocrine-Related Cancer has gathered together nine papers, where each article in some way reflects on how understanding the role of inherited and acquired changes to DNA has affected our understanding of endocrine neoplasia. Indeed, the transformation is quite stunning. Despite these transformative changes, the power of genomics continues to reveal deeper relations between otherwise seemingly unrelated entities, and the differences between clinically similar disorders are being understood at a genomic level. For clinicians, the key question is – what can I do with this information? We now know how knowledge of DNA variation at the individual level can significantly affect management at each stage – prevention, diagnosis and treatment. These reviews are focused on these aspects.

If we are going to start with a gene that is associated with an endocrine syndrome, let’s start with PTEN, as the Editor-in-Chief’s prerogative! Charis Eng, writing with Lamis Yehia, brings almost 23 years of DNA-based research knowledge to bear on the syndrome associated with germline alterations in PTEN, usually referred to as PTEN Hamartoma Tumor Syndrome (PHTS) (Yehia & Eng 2018). In addition to a very comprehensive review of PHTS, the authors draw attention and give name to a more recently appreciated set of conditions – the PTENopathies – which are the collection of disorders caused by alterations in genes downstream of PTEN, such as those encoding PI3K/AKT and mTOR. PTEN is to PTENopathies as BRCA1/2 are to other homologous recombination repair genes – similar but different, with similar opportunities for therapeutic intervention. Much new data are summarized.
When it comes to therapy, there is nothing more exciting in DNA-based genomic medicine than the promise of gene editing. Joanne Ngeow and colleagues (Tan et al. 2018) introduce the controversial idea of gene editing as an early intervention and treatment for hereditary cancers. While TALENs and Zinc Finger Nucleases may have had their day, the CRISPR-Cas9 system is taking the world by storm and is already the subject of at least one high profile patent battle, and many scientific prizes. The authors summarize how this form of gene editing could be used to inactivate gain-of-function alleles, or to restore lost functions of tumor suppressor genes. The technical, financial and ethical challenges are discussed.

Turning to more conventional approaches to endocrine tumor management, Luis Syro and colleagues (Syro et al. 2018) focus on one question: how and when should the potent alkylating chemotherapeutic agent temozolomide be used in treating pituitary carcinomas and aggressive pituitary adenomas? Pituitary carcinomas are of course very rare, so few endocrinologically inclined oncologists will have treated more than a few cases, making this review essential reading for these specialists. According to the authors, about 160 cases of aggressive pituitary adenomas and carcinomas have been treated with temozolomide. For pituitary carcinomas, temozolomide is probably the first choice, with responses of 50–87% to be expected. The decision of when to start the drug is evidently more difficult for adenomas.

Non-coding RNAs remain an under-explored area of cancer research. In a recent review published in the April issue of Endocrine-Related Cancer, Carolyn Klinge (Klinge 2018) gave us a whistle-stop tour of a complex field, with emphasis on the mysterious long non-coding RNAs. She includes in her review a very useful, fully referenced supplementary table including all your favorite endocrine tumor-related miRNAs. Something for the experts to read and digest.

The development of genomics to study genetic or epigenetic alterations at the pan-genomic level in a single experiment had a dramatic impact on the vision of cancer. In the specific field of endocrine tumors as described by Tom Giordano (Giordano 2018), who played a major role in various international programs dedicated to the integrated genomics characterization of several endocrine cancers, this clearly revealed new tumor classifications. New pathogenic mechanisms (new gene, chromosomal alterations, epigenetic changes, etc.) have been discovered with a fascinating increasing speed and the main findings are very well summarized. As explained in Tom Giordano’s review, this undoubtedly changed patient management and opens fascinating new perspectives.

The paradigm for endocrine neoplasia genetics begins with multiple endocrine neoplasia type 2 (MEN 2), reviewed by Lois Mulligan (Mulligan 2018), who was a co-discoverer of the first proto-oncogene cancer predisposition gene. This showed the way in molecular diagnosis, genotype–phenotype correlations and finally, medical management. Progress in the genetics of pheochromocytoma, a component of MEN 2, has been impressive this last 15 years. As a result, more than ten genes responsible for hereditary pheochromocytomas have been described. This clearly modifies clinical perspectives, as we now know that more than a third of pheochromocytomas are of genetic origin. In his review, Hartmut Neumann and colleagues (Neumann et al. 2018), who together with a large group of coworkers world-wide played a major role in merging pheochromocytoma clinical expertise with genetics for patient management, describes with enthusiasm the benefit of this progress for patient management. The genetic information changes our view of medical management for diagnosis, treatment and patient follow-up.

The list of genes responsible for endocrine tumors in children and adolescents is now impressive. Constantine Stratakis and William Foulkes played a major role in identifying and characterizing several of these genes. In the review co-authored with their US and Canadian collaborators (Goudie et al. 2018) this complex and evolving field is efficiently summarized. It clearly shows that almost all endocrine glands have been found to possess genetic alterations in at least one tumor susceptibility gene. Some of them are associated with multiple types of tumors; others are quite specific to a given endocrine gland. This review clearly illustrates how the role of the endocrine oncologist is a fascinating but challenging exercise to identify in a given patient the causative gene, and to personalize patient management according to the genetic knowledge.

The most important person in all this work is of course the person with the genetic problem. Ilene Sussman (Sussman 2018), writing for the VHL Alliance, beautifully summarizes the real meaning of DNA for many families – that of hope. Creatively, she also uses HOPE as an acronym for Health, Optimism, Perseverance and Encouragement, something that the VHL Alliance has been advocating for many years.

All of us who have contributed to the field of genomic medicine often take progress for granted,
or forget to appreciate advances, because we are all so focused on working hard for the patients and families. Therefore, reading this special issue is a very pleasant way to realize how much progress has been made in the field of endocrine tumors, thanks to all the methods and knowledge resulting from the initial discovery of DNA.

Progress has been spectacular; we now realize its impact in the everyday clinic for endocrine tumors patient management. However, this movement is accelerating almost every day, and undoubtedly, more impressive therapeutic progress will come as a result in the near future.

“We must not, in trying to think about how we can make a big difference, ignore the small daily differences we can make which, over time, add up to big differences that we often cannot foresee.”

– Marian Wright Edelman

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