THEMATIC REVIEW

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Classification of endocrine tumors in the age of integrated genomics

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Abstract

The classification of human cancers represents one of the cornerstones of modern pathology. Over the last century, surgical pathologists established the current taxonomy of neoplasia using traditional histopathological parameters, which include tumor architecture, cytological features and cellular proliferation. This morphological classification is efficient and robust with high reproducibility and has served patients and health care providers well. The most recent decade has witnessed an explosion of genome-wide molecular genetic and epigenetic data for most cancers, including tumors of endocrine organs. The availability of this expansive multi-dimensional genomic data, collectively termed the cancer genome, has catalyzed a re-examination of the classification of endocrine tumors. Here, recent cancer genome studies of various endocrine tumors, including those of the thyroid, pituitary and adrenal glands, pancreas, small bowel, lung and skin, are presented with special emphasis on how genomic insights are impacting endocrine tumor classification.

Key Words

- ▶ neoplasia
- ▶ neuroendocrine tumors
- ▶ molecular genetics
- ▶ thyroid
- ▶ adrenal cortex

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Introduction

Human cancers are genomic diseases characterized by germline and somatic genetic defects that drive and define the neoplastic phenotype (Stratton *et al.* 2009), which includes the ability of transformed cells to invade adjacent normal tissues and metastasize to distant sites (Hanahan & Weinberg 2011). Identifying and understanding the cellular and molecular consequences of these mutations has been one of the areas of intense focus in cancer research for the last several decades. These efforts were greatly accelerated by sequencing the human genome (Lander *et al.* 2001, Venter *et al.* 2001). Subsequently, during the most recent decade, the genomes of the most

common types of human cancer have been elucidated and characterized, largely due to remarkable advances in next-generation sequencing technologies (Metzker 2010, Goodwin *et al.* 2016, Levy & Myers 2016). Coordinated cancer genome discovery and characterization efforts by multi-disciplinary networks of investigators, such as The Cancer Genome Atlas (TCGA; <https://cancergenome.nih.gov>) (McCain 2006, Cancer Genome Atlas Research 2013, Wang *et al.* 2016) and the International Cancer Genome Consortium (ICGC; <https://icgc.org>) (Zhang *et al.* 2011, Jennings & Hudson 2013), as well as numerous institutional studies, have systematically addressed most

common cancers, as well as some rare types. Collectively, these integrated, multi-dimensional genomic studies have permitted a re-evaluation of human cancer at the most fundamental level, i.e. pathologic tumor classification, which has been traditionally based on histopathology. In many tumor types, these studies have confirmed existing tumor taxonomies, which in fact are the expected results since the morphology of a given tumor reflects its cumulative genetic and epigenetic changes. However, in most tumors, analysis of genomic data has revealed previously unrecognized molecular heterogeneity within pathologic entities and catalyzed significant refinements of tumor classification schemes. Together with the identification of novel genetic alterations, these results have profound implications for the treatment of cancer patients.

Tumors of endocrine organs are similarly genomic diseases. Compared to more common cancers, endocrine tumors sometimes do not attract equal attention and resources largely due to their relative rare nature. Fortunately for these patients, many endocrine cancer types have been investigated as part this genomic revolution. Here, the primary genomic studies of endocrine tumors will be reviewed, with special emphasis on those studies with significant taxonomic implications.

Power of integrated genomic analysis

Initially, the majority of genome-wide genetic and epigenetic studies interrogated a single molecular component of the cancer genome, such as the transcriptome, methylome or compendium of copy number alterations. While these single-platform studies have successfully advanced our knowledge of many cancer types, the availability of multi-platform molecular data on the same tumor cohort permits a higher level of analytical integration, which yields greater understanding of tumorigenesis and enhanced hypothesis generation. For example, the TCGA thyroid cancer study (Cancer Genome Atlas Research Network 2014) confirmed increased expression of an oncogenic microRNA (*mir-21*) in tumors with *BRAF*^{V600E} mutation and aggressive histologic features. However, by incorporating DNA methylation data, which revealed altered methylation of the *mir-21* promoter, a hypothesis was generated in which epigenetic regulation of microRNAs plays a role in the development of aggressive forms of *BRAF*^{V600E}-mutated thyroid cancer. Another such example from the TCGA adrenal cortical carcinoma project (Zheng *et al.* 2016) combined telomere length data with genotype, gene expression and copy

number data to extract critical insights into the role of telomere maintenance and whole-genome doubling in these cancers. Such sophisticated bioinformatic analyses are not possible when only single-platform molecular data are available. As such, the true power of the TCGA, ICGA and similar integrated genomic characterization studies lies in their ability to leverage multi-dimensional genomic data to derive novel insights into the molecular underpinnings and classification of cancer.

Thyroid cancer

Follicular cell-derived carcinomas

Tumors of the thyroid gland derived from follicular cells are broadly divided into differentiated and undifferentiated subtypes. Differentiated thyroid cancer includes papillary thyroid carcinoma (PTC) and its many histological variants, follicular thyroid carcinoma (FTC) and Hurthle cell (oncocytic) carcinoma. The remaining tumors are classified as either poorly differentiated thyroid carcinoma (PDCA) or anaplastic thyroid carcinoma (ATC) depending on their histology and degree of thyroid-related gene expression. By definition, ATC has essentially lost all of its follicular cell differentiation; hence, its alternative designation of undifferentiated thyroid carcinoma. Despite the prognostic significance of the differentiated vs undifferentiated taxonomy, it is now fully recognized that such a coarse classification scheme is inadequate to capture the full clinicopathologic and genetic diversity seen across thyroid cancers.

PTC represents the most common follicular cell thyroid cancer (Kitahara & Sosa 2016). As such, it was selected for study by TCGA for its project on thyroid cancer. The study cohort included 496 primary tumors analyzed using their standardized molecular platforms that included whole exome DNA sequencing, RNA sequencing, microRNA sequencing, copy number analysis, DNA methylation profiling and proteomic profiling (Cancer Genome Atlas Research Network 2014, Giordano 2014). For the sake of simplicity, PTCs were histologically classified into one of three main subtypes: classical type, tall cell variant and follicular variant.

Despite the fact that PTC is a relatively indolent cancer with an excellent overall prognosis and survival, many insights were nonetheless derived from its genomic characterization (Fig. 1). PTC was observed to have an overall low tumor mutational burden (Table 1) and a stable genome with few copy number alterations. Prevalent somatic alterations included *BRAF*^{V600E}, *RET* and

Figure 1

Genomic landscape of papillary thyroid carcinoma. (A) Tumor mutational burden. (B) Various molecular and clinicopathological features. (C) Number and frequency of recurrent somatic mutations. (D) Number and frequency of gene fusions. (E) Number and frequency of copy number alterations. (F) Types of driving alterations across the cohort. Reproduced, with permission, from [Cancer Genome Atlas Research Network \(2014\)](#).

other tyrosine kinase gene fusions and *RAS* family point mutations. These mutations were almost entirely mutually exclusive, which strongly suggests that possessing more one of these driver mutations does not provide a biological

advantage. The mutual exclusive nature of *BRAF*^{V600E} and *RAS* mutations permitted the development of a *BRAF*^{V600E}-*RAS* score, termed BRS, which was derived from distinct gene expression profiles of a selected 71-gene set.

Table 1 Tumor mutational burden across the spectrum of endocrine cancers.

Endocrine tumor type	Tumor mutational burden, mean	Tumor mutational burden, range	References
	Mean, non-silent mutations per MB	Range, non-silent mutations per MB	
Papillary thyroid carcinoma	0.41	0.00–2.158	Cancer Genome Atlas Research Network (2014)
Poorly differentiated thyroid carcinoma	>PTC	Unknown	Landa et al. (2016)
Anaplastic thyroid carcinoma	>>>PTC	Unknown	Landa et al. (2016)
Pituitary adenoma	0.6	0.14–4.42	Bi et al. (2017b)
Pancreatic NETs	0.82	0.04–4.56	Scarpa et al. (2017)
Small intestinal NETs	0.77	0.13–2.51	Francis (2013)
Adrenal cortical carcinoma	0.9	0.2–14.0	Zheng et al. (2016)
Pheochromocytoma/paraganglioma	Low	Unknown	Fishbein et al. (2017)
Small cell lung carcinoma	8.62	Unknown	George et al. (2015)
Merkel cell carcinoma, MCPyV negative	10.09	Unknown	Harms et al. (2015)
Merkel cell carcinoma, MCPyV positive	0.4	Unknown	Harms et al. (2015)

The BRS was used as a framework to visualize the entirety of the genomic data and interrogate the biology of the non-*BRAF*^{V600E} and non-RAS somatic mutations (Fig. 2). Using this approach, PTCs were divided into two broad groups, termed *BRAF*^{V600E}-like and RAS-like. This overarching result illustrates the striking biological differences between *BRAF*^{V600E}-like and RAS-like PTCs. This result correlated to a high degree with tumor morphology, in which *BRAF*^{V600E}-like PTCs are pathologically characterized by the presence of true papillae (classical type PTC) or tall cell features (tall cell variant PTC) and, conversely, RAS-like PTCs are distinguished by a pure follicular morphology without papillae or tall cell features (follicular variant PTC). Beyond the *BRAF*^{V600E}-like and RAS-like distinction, it became possible to further divide the *BRAF*^{V600E}-like group into two groups defined by *BRAF*^{V600E} and *RET* plus other gene fusions. While these observations match well with numerous existing studies (Zhu *et al.* 2003, Adeniran *et al.* 2006, Brzezianska *et al.* 2007, Koperek *et al.* 2012), the size of the TCGA cohort and the strength and

scope of the resulting data were enough to catalyze a deeper recognition and understanding of the different histologic and molecular subtypes of PTC. These insights have broad implications for pathology practice, clinical trial design and routine clinical care (Fagin & Wells 2016).

The overarching conclusion from the TCGA study raises the fundamental question of whether *BRAF*^{V600E}-like and RAS-like PTCs belong together as a single diagnostic entity. One alternative classification would be to reclassify RAS-like PTCs as FTCs because of their shared follicular growth pattern and predominance of RAS mutations (Esapa *et al.* 1999, Gupta *et al.* 2013, Medici *et al.* 2015). The significance of such a classification revision would impact many aspects of thyroid cancer care, including risk assessment and use of radioiodine (Asa *et al.* 2015).

FTCs have also been genomically investigated, but to a lesser degree given their rare incidence compared to PTC. A recent study of follicular adenomas and FTCs revealed similar tumor mutational burdens and evolutionary ages, suggesting a close pathogenetic relationship (Jung *et al.*

Figure 2

The *BRAF*^{V600E}-RAS score (BRS). (A) Ranking of papillary carcinoma according to the BRS. (B) Driver mutational status. (C) Thyroid differentiation score. (D) Genomic platform clusters. (E) Histologic type and follicular fraction. Reproduced, with permission, from Cancer Genome Atlas Research Network (2014).

2016). This result is generally consistent with another recent study of minimally invasive, angioinvasive and widely invasive FTCs that demonstrated similar genomic features, including tumor mutational burden. Despite this similarity, mutational burden was an independent predictor of structural recurrence and mortality (Nicolson *et al.* 2018).

The newly described follicular cell entity termed noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) defines a pure follicular neoplasm that is encapsulated or circumscribed without capsular or lymphovascular invasion and displays the nuclear features of papillary carcinoma (Nikiforov *et al.* 2016). NIFTPs, when properly diagnosed, have an exceptionally low risk of structural recurrence and accordingly were proposed as a new diagnostic entity to remove ‘carcinoma’ from the diagnostic nomenclature, thereby addressing in part the issue of thyroid cancer overdiagnosis (Brito & Hay 2017). NIFTPs are predominantly characterized by *RAS* mutations and therefore are considered to be *RAS*-like tumors (Paulson *et al.* 2017, Zhao *et al.* 2017, Kim *et al.* 2018b). Some preliminary gene expression data suggest that NIFTPs can exist in two forms, one similar to follicular adenomas and another similar to invasive follicular variants of PTC.

Recent genomic studies of PDCA have replicated the *BRAF*^{V600E}-like and *RAS*-like distinction observed in PTC, in addition to demonstrating an increased mutational burden (Table 1) (Landa *et al.* 2016). Regarding this distinction, a strong correlation with the type of PDCA was evident. PDCAs have been previously classified into two distinct histologic types. The Turin-type of PDCA is defined by growth pattern (e.g. insular) and mitotic rate (Volante *et al.* 2007, 2016). Conversely, the Memorial Sloan Kettering (MSK)-type of PDCA is defined on the basis of necrosis and mitotic rate, without an insular growth pattern (Hiltzik *et al.* 2006). In the Landa *et al.* study, *RAS*-like tumors were predominantly Turin-type (insular) PDCAs, whereas *BRAF*^{V600E}-like tumors were enriched for MSK-type (non-insular) PDCAs. Thus, the available genomic data support two distinct types of PDCA with strong histological association and distinct patterns of metastasis in which the *RAS*-like tumors often present with distant metastatic disease, and *BRAF*^{V600E}-like tumors with regional lymph nodes.

The Landa *et al.* study also analyzed a cohort of ATC. Collectively, ATCs displayed a higher overall mutational burden (Table 1) compared to PTC and PDCA, with significantly higher rates of *TERT* promoter mutations. Regarding the *BRAF*^{V600E}-like and *RAS*-like distinction

observed in PTC and PDCA, all of the ATCs had a *BRAF*^{V600E}-like phenotype irrespective of their genotype. This result may reflect a combination of a greatly increased tumor mutational burden and the presence of intratumoral inflammatory cells (i.e. macrophages) that together effectively eclipse the *BRS* gene expression signature. The collective insights derived from these studies are summarized in Fig. 3 (Giordano 2018).

Medullary carcinoma

The genetic landscape of medullary thyroid carcinoma (MTC) is distinct from follicular cell derived thyroid cancers (Ciampi *et al.* 2017). MTC is divided into heritable (30%) and sporadic (70%) forms and is characterized by germline and somatic point mutations of the *RET* proto-oncogene, respectively (Accardo *et al.* 2017). *RET*-negative MTCs contain *RAS* mutations (Ciampi *et al.* 2013) and rare *RET* fusions (Grubbs *et al.* 2015). Rare *ALK* fusions have also been identified by genomic studies (Ji *et al.* 2015). Recent immunohistochemical work suggests that loss of *RB* is associated with decreased survival (Valenciaga *et al.* 2017). To date, an integrated, multi-dimensional genomic characterization of MTC that sheds light on tumor classification has not been reported.

Pituitary adenoma and carcinoma

Genomic evaluation of pituitary adenomas, the most common CNS neoplasm (Theodros *et al.* 2015), is being deployed to refine their histological and molecular classification (Bi *et al.* 2018). Sporadic pituitary adenomas, similar to other low-grade endocrine tumors, are characterized by an overall low somatic tumor mutational burden (Table 1). Recurrently mutated genes in pituitary adenomas are enriched in a small number of pathways: cell cycle (*PIK3CA*, *NOTCH1/2*, and *GLI1/2/3*), chromatin modification and transcriptional regulation (*ARID1A/B*, *ASXL1*, *BRD4* and *CREBBP*) and DNA damage response (*PRKDC*, *BRCA1/2*, *ATM* and *FANCA*) (Bi *et al.* 2017a). Mutational patterns differ according to pituitary adenoma functional subtype, with mutations of the deubiquitinase *USP8* found in up to two-thirds of corticotroph adenomas (Ma *et al.* 2015, Reincke *et al.* 2015). Somatotroph adenomas contain frequent *GNAS* mutations (Ronchi *et al.* 2016, Bi *et al.* 2017a) and *GPR101*^{E308D} is found in a small number of acromegaly patients (Trivellin *et al.* 2014). *MEN1* mutations are found in both familial and sporadic cases (Uraki *et al.* 2017). Null cell adenomas have few recurrent point

Figure 3
Model of thyroid cancer pathogenesis and progression. Reproduced, with permission, from Giordano (2018).

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mutations, suggesting a role for alternative tumorigenic mechanisms such as copy number changes, gene fusions and/or epigenetic alterations. Indeed, chromosomal copy number changes have been identified and divide pituitary adenomas into two classes: a quiet group with few changes and a disrupted group with extensive arm-level genomic alterations (Bi *et al.* 2017a,b). Disrupted adenomas were associated with functional status, although there was no association between copy number status and atypical histology, Ki-67 proliferation index and recurrence (Bi *et al.* 2017a). Further clinical significance of this chromosomal classification awaits validation with larger cohorts.

Epigenetic changes are frequent in pituitary adenomas and exhibit subtype specificity (Farrell 2014). Epigenetic regulation may play a role in tumor cell invasion (Gu *et al.* 2016), although there is a lack of agreement between studies. A recent DNA methylation profiling study of null cell adenomas confirmed dysregulation of key pathways,

although differences between invasive and noninvasive tumors were minimal (Kober *et al.* 2018).

Exploration of the cancer genome of pituitary carcinoma has been limited by the extremely rare nature of this neoplasm (Yang *et al.* 2016). Pituitary carcinomas have been reported in patients with Lynch syndrome (Bengtsson *et al.* 2017) and *SDHB* mutations (Tufton *et al.* 2017), but an integrated genomic analysis of these tumors has not been reported.

Adrenal tumors

Adrenal cortical tumors

Adrenal cortical tumors are pathologically classified as adrenal cortical adenomas when they lack malignant potential, whereas those tumors that possess malignant potential are diagnosed as adrenal cortical carcinoma (ACC). The pathological assessment of malignant potential

is straightforward for the majority of tumors using established clinical and histopathological parameters that are often combined into one of several diagnostic systems (e.g. Weiss system (Weiss 1984)). Occasional tumors defy classification and can be diagnosed as adrenal cortical tumors of uncertain malignant potential.

Genomic information has greatly expanded the understanding of adrenal cortical tumors, which has led to increased personalized care of patients with ACC (Assie *et al.* 2014a). Moreover, molecular data derived from genomic studies generally correlate with histological parameters, which has resulted in advances in routine pathological assessment of these tumors.

In the course of developing the above-mentioned diagnostic systems, it was recognized that tumoral mitotic rate could be the basis for a proliferation-based prognostic grading scheme, classifying ACCs as either low or high grade (Weiss *et al.* 1989). This simple two-class scheme was confirmed by studies of the cancer transcriptome using independent patient cohorts (de Reynies *et al.* 2009, Giordano *et al.* 2009) and has been largely accepted into routine pathology practice (Giordano 2011). Along similar proliferation-related lines, the Ki-67 proliferation index assessed by routine immunohistochemical staining has also been shown to have major prognostic significance (Morimoto *et al.* 2008, Beuschlein *et al.* 2015) and has also been recommended for routine practice via the most recent College of American Pathologists' protocol for examination of adrenal cortical tumors.

An integrated genomic characterization of 45 ACCs by the European Network for the Study of Adrenal

Tumors (ENSAT) (Assie *et al.* 2014b) identified novel genetic alterations (e.g. *ZNRF3*, *DAXX* and *TERT*) and provided strong support for a two-group classification with different patient outcomes. The poor outcome group, termed C1A, had a higher mutation burden and increased DNA methylation changes. In contrast, the good outcome group, termed C1B, had fewer mutations and was characterized by deregulation of microRNA clusters. Beyond the two-class system, the data suggested that methylation status might further divide the C1A group into different prognostic subgroups.

TCGA performed a similar integrated, multi-platform genomic analysis using a near-global cohort of 91 ACCs (Zheng *et al.* 2016), which confirmed many of the prior findings from the ENSAT study. This study identified a relatively higher tumor mutational burden (Table 1) and further extended the cohort of ACC driver mutations to include *PRKARI1*, *RPL22*, *TERF2*, *CCNE1* and *NF1* and illustrated the dominant role that copy number alterations, including whole-genome doubling, play in ACC pathogenesis and progression. Regarding ACC classification, three distinct outcome groups were identified using a cluster of cluster (COC) analysis of the complete set of genomic data (Fig. 4), which could be nearly replicated by a 68-CpG probe methylation signature. This COC solution also provided a context for the increased understanding of the different types of ACC. COC1 tumors largely corresponded to C1B tumors in the ENSAT study and had distinct genomic (e.g. transcriptional) profiles with a lower tumor mutational burden. COC2 and COC3 tumors corresponded to C1A tumors in the ENSAT

Figure 4

Cluster of cluster (COC) analysis of adrenal cortical carcinoma. (A) COC analysis using data from four genomic platforms. (B) Event free survival of the COC groups. Reproduced, with permission, from Zheng *et al.* (2016).

study and differed in transcriptional, methylation and copy number profiles. The TCGA study effectively divided the C1A group in the ENSAT study into two distinct prognostic subgroups. These collective findings are illustrated in Fig. 5.

Translation of this three-group ACC classification via an assay that can be performed with routinely available pathology materials, such as formalin-fixed paraffin-embedded tissue, is currently underway by several groups. The successful implementation of a routine clinical assay will represent a meaningful advance for the classification of ACCs by providing a more refined assessment of tumor biology and prognosis, with the potential to impact patient care.

Pheochromocytoma and paraganglioma

Tumors of the adrenal medulla and extra-adrenal paraganglia are highly related tumors with similar histological and genetic features. Pheochromocytoma is defined by the World Health Organization (WHO) as 'a tumor of chromaffin cells that arises in the adrenal medulla', whereas extra-adrenal paragangliomas are 'tumors originating from neural crest-derived paraganglion cells situated in the region of the autonomic nervous system ganglia and accompanying nerves' (Lloyd *et al.* 2017).

Pheochromocytomas and paragangliomas (PPGL) have a very high degree of heritability (up to 40% of patients) and are part of many hereditary syndromes (Dahia 2014, Favier *et al.* 2015). Innumerable studies have identified the

germline and somatic mutations that drive tumorigenesis (Turchini *et al.* 2018). However, the TCGA genomic characterization of PPGL extended the knowledge base of these tumors in several aspects, including the identification of novel mutations such as recurrent *MAML3* gene fusions and *CSDE1* frameshift and splice-site mutations (Fishbein *et al.* 2017). These mutations display a high degree of mutual exclusivity (Fig. 6), as observed in other endocrine tumors with relatively low mutational burdens, demonstrating a lack of clonal advantage of having more than one such mutation. Relevant to tumor classification, this study expanded the molecular taxonomy of PPGL by identifying a Wnt signaling group of tumors in addition to confirming the previously described molecular classes termed pseudohypoxia (Jochmanova *et al.* 2015) and kinase signaling (Bjorklund *et al.* 2016). This three-group classification has significant implications for many aspects of PPGL diagnosis, risk assessment and treatment, as summarized in Fig. 7.

Neuroblastoma

Neuroblastoma belongs to a group of neuroblastic tumors that arise from the sympathoadrenal lineage of the neural

crest. These tumors represent a wide range of tumor biology that spans from benign (ganglioneuroma) to malignant tumors (ganglioneuroblastoma and neuroblastoma). Neuroblastoma is characterized by variable clinical behavior and response to therapy. Decades ago, it was discovered that amplification of the *MYCN* oncogene identified a minority of neuroblastomas with high-risk disease (Schwab *et al.* 1984), and *MYCN* amplification status remains a clinically relevant biomarker (Westermarck *et al.* 2011). Beyond *MYCN* alterations, other somatic mutations are relatively rare (Molenaar *et al.* 2012, Pugh *et al.* 2013) and include *ALK* amplification and point mutations of *ALK*, *ATRX*, *PTPN11*, *TIAM1* and *ARIA1A/B* (Sausen *et al.* 2013, Bresler *et al.* 2014).

Genome-wide evaluation of chromosomal copy number alterations confirmed and extended the *MYCN*-based molecular classification (Janoueix-Lerosey *et al.* 2009). Similar to ACCs, tumors characterized with arm-level chromosomal changes were associated with a favorable outcome compared to high-risk tumors that possessed more segmental alterations, with an observed correlation between outcome and the number of segmental alterations (Schleiermacher *et al.* 2010).

Figure 6

Germline and somatic genetic alterations in pheochromocytoma and paraganglioma. Reproduced, with permission, from Fishbein *et al.* (2017).

Figure 7

Molecular classification of pheochromocytoma and paraganglioma. Corresponding driver mutations, proportions of hereditary disease, key altered pathways, locations, degrees of paraganglial cell differentiation and risk of malignant behavior. Reproduced, with permission, from [Crona et al. \(2017\)](#).

Transcriptome studies of neuroblastoma have identified several prognostic gene expression signatures that are independent of established prognostic factors ([Fardin et al. 2010](#), [De Preter et al. 2011](#), [Asgharzadeh et al. 2012](#), [Applebaum et al. 2016](#)), and some profiles using routinely available tissue sample are moving toward clinical implementation ([Stricker et al. 2014](#)). Collectively, these studies and others highlight some of the translational advances that are leading to improved molecular risk stratification and potential novel therapeutic approaches ([Bosse & Maris 2016](#)).

Pancreatic neuroendocrine tumors

The genomic landscape of pancreatic neuroendocrine (NE) neoplasms (PanNENs) has been significantly elucidated by recent studies ([Jiao et al. 2011](#), [Scarpa et al. 2017](#), [Wong et al. 2017](#), [Mafficini & Scarpa 2018](#)). Genetically, PanNENs are markedly distinct from more common primary pancreatic cancers, such as adenocarcinoma ([Jiao et al. 2011](#), [Cancer Genome Atlas Research 2017](#)).

PanNENs are broadly divided into well- and poorly differentiated groups, termed PanNETs and PanNECs, respectively. The WHO further classifies them into three grades (G1, G2 and G3). PanNETs are graded into G1, G2 or G3 groups based on proliferation, whereas PanNECs are uniformly graded as G3 tumors ([Lloyd et al. 2017](#)). PanNETs and PanNECs have significantly different genetic profiles, consistent with their distinct clinical behavior. PanNETs possess an indolent growth and have a relatively low tumor mutational burden ([Table 1](#)) ([Scarpa et al. 2017](#)). Beyond some of the initial genes to be identified in PanNETs, such as *MEN1* ([Gortz et al. 1999](#)), genomic studies have expanded the universe of somatic driver genes to include *DAXX*, *ATRX*, *TSC1/2*, *PTEN*, *NF1*, *DEPDC5* and *EWSR1* gene fusions ([Jiao et al. 2011](#), [Scarpa et al. 2017](#)). Classification of PanNETs based on mutational profiles has identified four core pathway-related groups: DNA damage repair, chromatin remodeling, mTOR signaling and altered telomere maintenance. Regarding prognostic grading, some of these PanNETs classes have been associated with distinct clinical behavior. Overall, PanNETs with *MEN1* and *DAXX/ATRX* mutations have a

better prognosis (Jiao *et al.* 2011), although intermediate-grade (G2) PanNETs with *DAXX/ATRX* mutations have a poor prognosis within this grade group (Scarpa *et al.* 2017). Tumors without altered telomere length were associated with a better outcome (Scarpa *et al.* 2017). While these associations need further validation with larger cohorts, the collective data suggest that mutational status possesses significant prognostic information for PanNETs.

In addition to the pathway-based classification of PanNETs, it was possible to identify five types of tumors based on mutational signatures (Scarpa *et al.* 2017), including a novel signature termed *MUTYH* inactivation because of biallelic inactivation of *MUTYH* (germline-inactivating mutations combined with simultaneous deletion of the other allele). Other observed signatures included BRCA, APOBEC and AGE. It is clear from the collective genomic data that PanNETs, as a group, contain significantly more molecular heterogeneity than predicted based on histology alone.

PanNECs have distinct genetic profiles from PanNETs, with frequent mutations in *TP53*, *RB1* and *CDKN2A* and *DAXX/ATRX* mutations are notably absent in the high-grade carcinomas regardless of their small-cell or large cell histology (Yachida *et al.* 2012). These genetic differences support the classification of PanNECs as high-grade (G3) neoplasms, defined on the basis of proliferation activity (>20 mitoses per 10hpf or a Ki-67 proliferation index of >20%) in the WHO classification of PanNENs (Lloyd *et al.* 2017).

Small intestinal neuroendocrine tumors

Neuroendocrine tumors of the small intestine (SINETs) represent the most common small intestinal cancer and are increasing in incidence (Yao *et al.* 2008). Similar to other low-grade endocrine tumors, genomic studies have revealed a relatively low mutational burden (Table 1) (Banck *et al.* 2013, Francis *et al.* 2013). Genomic studies have identified few recurrent alterations, including loss of heterozygosity at chromosome 18 (Cunningham *et al.* 2011), arm-level chromosomal gains (Kulke *et al.* 2008) and mutations of *CDKN1B* (Francis *et al.* 2013). An integrated genomic study of SINETs revealed significant molecular diversity within SINETs and divided tumors into three groups based on *CDKN1B* mutational status, epigenetic profiles and copy number profiles (Karpathakis *et al.* 2016). Importantly, these molecular groups were associated with distinct survival. This provocative study awaits validation and translation to routine practice.

Lung neuroendocrine tumors

Neuroendocrine tumors of the lung represent a biologically diverse set of related tumors that are distinct from non-small-cell lung carcinomas, such as adenocarcinoma and squamous cell carcinoma. Neuroendocrine tumors are classified into three main groups based on histological features. Low-grade neuroendocrine tumors, termed typical carcinoids (TCs) and intermediate-grade neuroendocrine tumors, termed atypical carcinoids (ACs) are histologically and molecularly distinct from high-grade neuroendocrine tumors, which are divided into small-cell (SCLC) and large-cell (LCLC) types. The collective molecular data support this existing histological classification, with carcinoids and carcinomas displaying distinct mutational burdens and profiles (Swarts *et al.* 2012, Simbolo *et al.* 2017). For example, somatic *TP53* mutations and loss of 3p are common in NE carcinomas, yet rare in carcinoids (Rossi *et al.* 2018). These molecular differences are directly related to differences in tobacco exposure, which is known to cause *TP53* and other mutations (Gibbons *et al.* 2014). In contrast, *MEN1* mutations are nearly exclusively present in carcinoids (Simbolo *et al.* 2017).

A genomic study of a large cohort of small-cell carcinomas revealed a high mutational burden with bi-allelic inactivation of *TP53* and *RB* in nearly all cases, suggesting that loss of these tumor suppressors is an obligatory event in this tumor (George *et al.* 2015). In addition, kinase mutations and *NOTCH* family mutations were frequent. Unsupervised hierarchical clustering of transcriptome data identified two classes with distinct gene expression profiles of various NE markers, yet similar mutational profiles. These classes reflected differing levels of NOTCH pathway activation and may form the basis for a future molecular classification of SCLC. This comprehensive study, supported by mouse studies, provides evidence that *NOTCH* functions as a tumor suppressor and master regulator of NE differentiation in SCLC.

Skin neuroendocrine tumors

Primary cutaneous neuroendocrine carcinoma, termed Merkel cell carcinoma (MCC), is a rare, clinically aggressive neoplasm with a high mortality rate (Llombart *et al.* 2017). The incidence of MCC has increased dramatically in recent decades, especially in elderly patients with significant sun exposure. Histologically, it shares features with small-cell carcinoma of the lung, although some MCC contain a mixed non-neuroendocrine component

such as squamous cell carcinoma. Molecularly, MCC can be divided into two etiologically distinct groups. One group is characterized by viral integration of Merkel cell polyomavirus that contributes to MCC tumorigenesis by suppressing *RB* via inhibition by large T antigen (Feng *et al.* 2008). In contrast, the other group lacks Merkel cell polyomavirus and is characterized by UV light-mediated mutations, such as frequent *TP53*, *RB1*, and *NOTCH* mutations. These two MCC classes are biologically and clinically distinct, with differing tumor mutational burdens (Table 1) and landscapes (Harms *et al.* 2015, Goh *et al.* 2016), copy number profiles (Paulson *et al.* 2009), and outcomes, with viral cases carrying a better prognosis. The collective evidence suggests that these two MCC groups arise from different cells, with viral-negative and viral-positive tumors arising from epidermal keratinocytes and dermal fibroblasts (Harms *et al.* 2015), respectively, although this awaits validation.

Significance of mutational burden

From the collective available information on tumor mutational burden across endocrine tumors (Table 1), a clear relationship between tumor mutational burden and tumor behavior emerges. While this relationship is generally found across all cancers, and tumor mutational burden is increasingly recognized as an important genomic metric (Chalmers *et al.* 2017) that can predict response to immunotherapy (Goodman *et al.* 2017, Yarchoan *et al.* 2017, Steuer & Ramalingam 2018), it may be especially relevant and revealing in endocrine neoplasia (Hellmann *et al.* 2018, Kim *et al.* 2018a). Many genomic assays have incorporated measurements of tumor mutational burden, and it will be interesting to see what role it might play in endocrine tumor evaluation and patient care in the coming years.

Therapeutic implications of genomic characterization of endocrine tumors

Advances in genomic characterization of human cancers have identified 12 core signaling pathways that serve to regulate essential cellular functions, including cell fate and survival and maintenance of the genome (Vogelstein *et al.* 2013). The classification of human cancer has the potential to evolve toward a pathway-based taxonomy, thereby supplementing the existing organ-based approach (Sanchez-Vega *et al.* 2018). This transformation has already begun with the approval of immunotherapies (i.e. pembrolizumab) based on genetic

alterations (e.g. mismatch repair defects) independent of tumor origin or histology (Le *et al.* 2015). This pathway-based approach is being applied to endocrine tumors (e.g. ACC) and will likely accelerate in the coming years, although the existing cell-of-origin taxonomy retained its biological significance in a TCGA pan-cancer analysis of 33 cancer types (Hoadley *et al.* 2018). This suggests that cell-of-origin context will be a significant factor in therapeutic response to targeted therapy, independent of genotype, signaling pathway activation and other genomic features.

Conclusion

Coordinated genomic discovery programs like TCGA and ICGC are characterizing the cancer genome for many cancer types, including endocrine tumors. The last decade has seen significant accomplishments that can be broadly divided into improved understanding of the molecular basis of cancer, revised tumor classification schemes through discovery of novel molecular subtypes, and identification of genomic attributes of tumors that can serve as therapeutic targets and predictors of response. The availability of robust molecular classification schemes for endocrine cancers is leading to advances in the diagnosis, prognostication and treatment of these patients.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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