4 THE DISPERSED ENDOCRINE SYSTEM

Neuroendocrine cells are found throughout the body in many sites. In some classical endocrine organs, such as pituitary and parathyroid, they comprise the main parenchymal element. In others, such as thyroid, the neuroendocrine component (C cells) represent a small minority of an endocrine gland that is predominantly not neuroendocrine. However, the major mass of neuroendocrine cells is distributed in non-endocrine tissues where they are known as the dispersed endocrine system. This chapter will deal with the epithelial neuroendocrine cells of the head and neck, of the thorax and abdomen, where they are scattered in thymus, lung, and gastroenteropancreatic tract, and of the pelvis, where they are found in the genitourinary system including the gonads.

The common features of neuroendocrine cells are structural and functional. Structurally they all have well developed rough endoplasmic reticulum that is required for their main function, hormone synthesis (fig. 4-1). They generally have large Golgi complexes where hormone packaging takes place and they contain variable numbers of highly characteristic secretory granules that represent packaged hormone product within a double membrane that can fuse to the cell surface, releasing hormone (1). These cells express synaptophysin (and its related proteins synaptopbrevin, synaptotagmin and synapsin) and chromogranins, as well as other less specific biomarkers such as neuron specific enolase, CD56 and CD57. Because they are epithelial, they generally express keratins, allowing identification with AE1/AE3 or Cam 5.2; this is in contrast to paragangliomas that are negative for keratins (2) and are discussed in chapter 5. Other biomarkers, including transcription factors, hormones and enzymes, are expressed by specific neuroendocrine cells, allowing their identification and

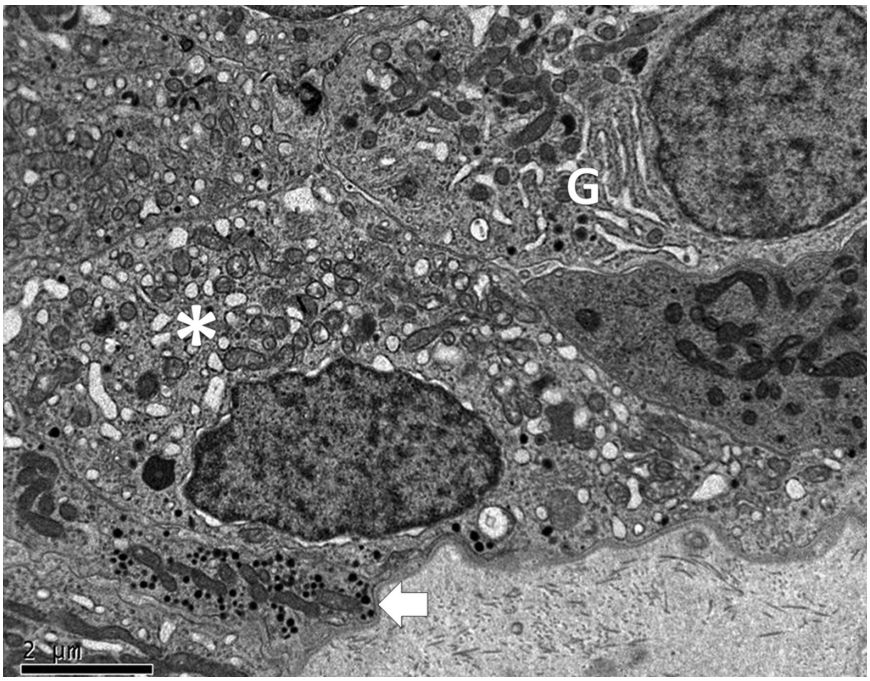

Figure 4-1

NEUROENDOCRINE NEOPLASMS

Neuroendocrine neoplasms are a family of tumors that share structural and functional cellular properties based on their ability to synthesize peptide hormones. The tumor cells have well developed rough endoplasmic reticulum (*) where hormone synthesis occurs, prominent Golgi complexes (G) where synthesized hormone is packaged into forming secretory granules, and mature secretory granules lined by double membranes and with variable contents (arrow) that store hormone until regulatory signals stimulate membrane fusion at the cell perimeter and release of hormone for local (paracrine) or distant (endocrine) action.

Table 4-1

BIOMARKERS OF NEUROENDOCRINE CELLS AND TUMORS

Location	Cell Type	Transcription Factor(s)	Hormones	Other
Hypothalamus	Neurons	NeuN, TTF1	GRH, TRH, CRH, GnRH, Dopamine, Somatostatin Vasopressin, Oxytocin	Neurofilaments
Pituitary	Corticotroph	Tpit, NeuroD1	ACTH, other POMC derivatives	Keratins (+++)
	Somatotroph	Pit1	GH	Keratins[a]
	Lactotroph	Pit1, ER	PRL	(Keratins)[b]
	Mammosomatotroph	Pit1, ER	GH, PRL	Keratins
	Thyrotroph	Pit1, GATA2/3	TSH	(Keratins)
	Gonadotroph	SF1, ER, GATA 2/3	FSH, LH	(Keratins)
Thyroid	C Cell	PAX8, TTF1	Calcitonin, CGRP	Keratins, CEA[a]
Parathyroid	Chief cell + variants	GATA3, GCM2	PTH	Keratins
Thymus	Unclassified NE cells	(TTF1, PAX8[c])	Calcitonin, CGRP	
Lung	P1. P2, P3	TTF1	Bombesin, Serotonin, Calcitonin, CGRP	Keratins (CEA[d])
Stomach	ECL	(CDX2)	Histamine	VMAT2, Keratins
	EC		Serotonin	Keratins
	D		Somatostatin	Keratins
	XP, D1		Xenin, Ghrelin	Keratins
Pancreas	A	PDX1, ISL1, CDX2	Glucagon	Keratins
	B		Insulin	Keratins
	D		Somatostatin	Keratins
	PP		Pancreatic polypeptide	Keratins
Bowel	G	*Duodenum:*	Gastrin	Keratins
	D	ISL1, PDX1, CDX2	Somatostatin	
	I		CCK	
	K	*Jejunum and Ileum:*	GIP	
	S	CDX2	Secretin	
	MO		Motilin	
	N		Neurotensin	
	L	*Colon:* (CDX2)	GLI, PYY, PP	Colon: PSAP
	EC		Serotonin	
Prostate, Kidney, Bladder, Gonads, Breast	Unclassified NE cells	Variable	Variable	Keratins (PSAP)
Skin	Merkel cell	PAX5	None	Dot-like CK20, Tdt Merkel polyoma virus
Paragangliomas		GATA3	Dopamine Adrenalin Noradrenaline	Tyrosine Hydroxyase, L-Dopa-Decarboxylase, Phenylethanolamine N-methyltransferase (PNMT)

[a]Pattern of keratin positivity distinguishes tumor types; see chapter 3.
[b]Items in brackets are not consistent findings in normal cells; tumors may have significant variability.
[c]PAX8 in thymic lesions is controversial and likely due to cross reactivity in polyclonal antisera.
[d]Using monoclonal antibody.

distinction (Table 4-1). It is important to note that tumors do not always read the textbooks and may not follow the rules! Aggressive tumors often express aberrant profiles, most notably TTF1 in high grade lesions but also CDX2, and ectopic hormone production, most commonly ACTH and α-subunit (identified with αhCG antisera), is another unifying feature of these tumors.