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Review

Molecular and cellular biology of neuroendocrine lung tumors: Evidence for separate biological entities

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ABSTRACT

Pulmonary neuroendocrine tumors (NETs) are traditionally described as comprising a spectrum of neoplasms, ranging from low grade typical carcinoids (TCs) via the intermediate grade atypical carcinoids (ACs) to the highly malignant small cell lung cancers (SCLCs) and large cell neuroendocrine carcinomas (LCNECs). Recent data, however, suggests that two categories can be distinguished on basis of molecular and clinical data, i.e. the high grade neuroendocrine (NE) carcinomas and the carcinoid tumors.

Bronchial carcinoids and SCLCs may originate from the same pulmonary NE precursor cells, but a precursor lesion has only been observed in association with carcinoids, termed diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. The occurrence of mixed tumors exclusively comprising high grade NE carcinomas also supports a different carcinogenesis for these two groups. Histopathologically, high grade NE lung tumors are characterized by high mitotic and proliferative indices, while carcinoids are defined by maximally 10 mitoses per 2 mm^2 (10 high-power fields) and rarely have Ki67-proliferative indices over 10%. High grade NE carcinomas are chemosensitive tumors, although they usually relapse. Surgery is often not an option due to extensive disease at presentation and early metastasis, especially in SCLC. Conversely, carcinoids are often insensitive to chemo- and radiation therapy, but cure can usually be achieved by surgery.

A meta-analysis of comparative genomic hybridization studies performed for this review, as well as gene expression profiling data indicates separate clustering of carcinoids and carcinomas. Chromosomal aberrations are much more frequent in carcinomas, except for deletion of 11q, which is involved in the whole spectrum of NE lung tumors. Deletions of chromosome 3p are rare in carcinoids but are a hallmark of the high grade pulmonary NE carcinomas. On the contrary, mutations of the multiple endocrine neoplasia type 1 (*MEN1*) gene are restricted to carcinoid tumors.

Many of the differences between carcinoids and high grade lung NETs can be ascribed to tobacco consumption, which is strongly linked to the occurrence of high grade NE carcinomas. Smoking causes p53 mutations, very frequently present in SCLCs and LCNECs, but rarely in carcinoids. It further results in other early genetic events in SCLCs and LCNECs, such as 3p and 17p deletions. Smoking induces downregulation of E-cadherin and associated epithelial to mesenchymal transition. Also, high grade lung NETs display higher frequencies of aberrations of the Rb pathway, and of the intrinsic and extrinsic apoptotic routes. Carcinoid biology on the other hand is not depending on cigarette smoke intake but rather characterized by aberrations of other specific genetic events, probably including Menin or its targets and interaction partners. This results in a gradual evolution, most likely from proliferating pulmonary NE cells via hyperplasia and tumorlets towards classical carcinoid tumors.

We conclude that carcinoids and high grade NE lung carcinomas are separate biological entities and do not comprise one spectrum of pulmonary NETs. This implies the need to reconsider both diagnostic as well as therapeutic approaches for these different groups of malignancies.

Contents

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1. Introduction

Neuroendocrine tumors (NETs) of the lung comprise a heterogenous population of tumors, ranging from well-differentiated bronchial carcinoids to highly malignant and poorly differentiated small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC) (Table 1). In classification systems lung NETs are often represented as a spectrum, and a number of 10 mitoses per 2 mm^2 (this usually equals 10 high power fields) is the criterium defined by the WHO to separate pulmonary carcinoids from neuroendocrine (NE) carcinomas [1]. However, in a clinicopathological sense they behave very differently. Virtually all SCLCs and LCNECs display much higher mitotic indices (average between 60 and 75 mitoses per 2 mm^2) and tumors with intermediate mitotic indices (10–20), most often classified as LCNECs, are rare [1]. They grow very rapidly and occur almost exclusively in patients with a history of smoking [2]. Lung carcinoids occur frequently in never-smokers and are subdivided into typical (TC) and atypical (AC) carcinoids [1,3]. TCs and SCLCs are more frequently found to be centrally located in the lung, while ACs and LCNECs more often show a peripheral localization [1].

This review will focus on the similarities and differences between carcinoids and high grade NE lung carcinomas, emphasizing on the molecular pathogenesis, and the present theories concerning the cell(s) of origin of these neoplasms. We will argue that pulmonary carcinoids represent a separate entity of lung NETs rather than being part of a continuum of NE neoplasms. This implies the need to reconsider lung NET diagnosis, where tumors with intermediate mitotic activity should be considered either low grade carcinoids or

Table 1
Clinicopathological and epidemiological characteristics of pulmonary neuroendocrine tumors and precursor lesions.

	DIPNECH	Tumorlet	TC	AC	LCNEC	SCLC	References
Mitoses per 2 mm^2 (10 HPF)	Absent	Absent	<2	2–10	>10 (median 70)	>10 (median 80)	[1,2,79]
Necrosis	Absent	Absent	Absent	Focal	Extensive	Extensive	[5]
Most frequent location	Peripherally	Peripherally	Centrally	Peripherally	Peripherally	Centrally	[1,86,87]
Mean age at diagnosis	50–60	60–70	40–50	50–60	68	50–70	[11,221,222]
Sex ratio (male:female)	1:4	1:>4	1:1	1:1/2:1	4:1/8:1	1:1	[10,11,221,223,224]
% of total number of lung cancers	NR	NR	1–2%	0.1–0.2%	1.6–3%	15–20%	[2,12]
% smokers	37%	Unknown	33%[a]	64%	98%	97%	[8,11,80,222]
5-Year overall survival	NR	NR	92–100%	61–88%	13–57%	5%	[5,12]
% lymph node metastasis	NR	Low	4–14%	35–64%	40%	90%	[5,84,225]
% distant metastasis	NR	Very low	1.5%	10%	65%	60–70%	[1,8,12,18,81]

Abbreviations used: AC, atypical carcinoid; DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; HPF, high power fields; LCNEC, large cell neuroendocrine carcinoma; NR, not relevant; SCLC, small cell lung cancer; and TC, typical carcinoid.

[a] Equal to the general population.