Identification of defined molecular subgroups based on immunohistochemical analyses and potential therapeutic vulnerabilities of pulmonary carcinoids

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Abstract

Introduction

Multi-omic studies have identified three molecularly separated pulmonary carcinoid (PC) subgroups (A1, A2, B) with distinctive *mRNA* expression profiles (e.g. OTP/ASCL1/HNF1A). We aimed to establish an immunohistochemical (IHC) biomarker panel that enables subgroup identification and assesses its potential clinical relevance.

Material and Methods

All patients with resected pulmonary carcinoids (2003–2012) were identified from the Dutch Cancer/pathology registry, and tumors were revised. The IHC expression of OTP/ASCL1/HNF1A was scored in a blinded fashion in mRNA-profiled (*n*=5 of each subgroup) and carcinoid cohort (*n*=478) including matching metastases of recurrent carcinoids (*n*=19). Potential therapeutic targets (SSTR2A/DLL3) were assessed. Normal lung tissue at distance and surrounding carcinoid tissue were evaluated for neuroendocrine cell hyperplasia (NECH). IHC was assessed using H-scoring.

Results

OTP/ASCL1/HNF1A showed similar IHC and mRNA expression patterns in the matched primary samples. In the national cohort IHC separated PC's into subgroups A1 [n=224 (53%), $OTP^{high}/ASCL1^{high}/HNF1A^{low}$], A2 [n=161 (38%), $OTP^{high}/ASCL1^{low}/HNF1A^{high}$], and B [n=37 (9%), $OTP^{low}/ASCL1^{low}/HNF1A^{high}$]. In 12% of PCs, no distinct classification could be provided. Patients with A1 were enriched for older age (83% >50y), females (83%), and peripheral location (55%) with low SSTR2A (median 10) and high DLL3 expression (median 52). A2 included younger patients (34% <40y) and endobronchial/central (87%) tumors with high SSTR2A (median 160), but low DLL3 (median 0) expression. B included more males (59%) and recurrence was more frequent in B (19%) than in A1 (8%) and in A2 (6%). Matching primary-metastatic tumors showed similar IHC expression patterns. Neuroendocrine cell hyperplasia was enriched in A1 (25%) compared with A2 (3%) and B (0%).

Conclusions

An OTP/ASCL1/HNF1A IHC panel enables the identification of molecular defined pulmonary carcinoid subgroups with distinct clinical phenotypes and diverging therapeutic vulnerabilities that require further prospective evaluation.