Lung neuroendocrine tumors: correlation of ubiquitinylation and sumoylation with nucleo-cytosolic partitioning of PTEN

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BACKGROUND
The tumor suppressor phosphatase and tensin homolog (PTEN) is a pleiotropic enzyme, inhibiting phosphatidyl-inositol-3 kinase (PI3K) signaling in the cytosol and stabilizing the genome in the nucleus. Nucleo-cytosolic partitioning is dependent on the post-translational modifications ubiquitinylation and sumoylation. This cellular compartmentalization of PTEN was investigated in lung neuroendocrine tumors (lung NET).

METHODS
Tumor tissues from 192 lung NET patients (surgical specimens = 183, autopsies = 9) were investigated on tissue microarrays. PTEN was H-scored by two investigators in nucleus and cytosol using the monoclonal antibody 6H2.1. Results were correlated with immunoreactivity for USP7 (herpes virus-associated ubiquitin-specific protease 7) and SUMO2/3 (small ubiquitin-related modifier protein 2/3) as well as PTEN and p53 FISH gene status. Clinico-pathologic data including overall survival, proliferation rate and diagnostic markers (synaptophysin, chromogranin A, Mib-1, TTF-1) were recorded.

RESULTS
The multicentre cohort included 58 typical carcinoids (TC), 42 atypical carcinoids (AC), 32 large cell neuroendocrine carcinomas (LCNEC) and 60 small cell lung carcinomas (SCLC). Carcinoids were smaller in size and had higher synaptophysin and chromogranin A, but lower TTF-1 expressions. Patients with carcinoids were predominantly female and 10 years younger than patients with LCNEC/SCLC. In comparison to the carcinoids, LCNEC/SCLC tumors presented a stronger loss of nuclear and cytosolic PTEN associated with a loss of PTEN and p53. Concomitantly, a loss of nuclear USP7 but increase of nuclear and cytosolic SUMO2/3 was found. Loss of nuclear and cytosolic PTEN, loss of nuclear USP7 and increase of cytosolic SUMO2/3 thus correlated with poor survival. Among carcinoids, loss of cytosolic PTEN was predominantly found in TTF1-negative larger tumors of male patients. Among SCLC, loss of both cytosolic and nuclear PTEN but not proliferation rate or tumor size delineated a subgroup with poorer survival (all p-values <0.05).
CONCLUSIONS
Cellular ubiquitinylation and sumoylation likely influence the functional PTEN loss in high grade lung NET. Both nuclear and cytosolic PTEN immunoreactivity should be considered for correlation with clinico-pathologic parameters.

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