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Lung neuro-endocrine 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 neuro-endocrine 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 p53FISH 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 neuro-endocrine 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.

Biography

Alex Soltermann is an Assistant Professor of the University of Zurich and consultant Surgical Pathologist at the Institute of Surgical Pathology, University Hospital Zurich, Switzerland, where he is responsible for lung and head neck pathology. He is also the head of *In-situ* IHC/FISH laboratory. His research is focused on the tumor-stroma interactions of lung squamous cell carcinoma and corresponding localized molecular analysis of tumor tissue using laser capture micro-dissection and micro-fluidic probes. Currently, he is working on a 3D tumor model using a combination of serial histologic sections and parallel X-ray micro-tomography. He has 72 original publications.

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