Molecular characterisation of pulmonary supra-carcinoids through integration of multi-omics data

Introduction to pulmonary carcinoids

• Pulmonary carcinoids (PCA), comprising typical and atypical carcinoids, are a group of low-grade lung neuroendocrine neoplasms that, unlike their high-grade counterparts, have relatively good prognosis and no known risk factors.

• Little is known about the recently described supra-carcinoid subtype. Supra-carcinoids are:
  - Morphologically similar to atypical carcinoids, with clinical and molecular features similar to high grade large cell neuroendocrine carcinoma (LCNEC).
  - Display higher expression of immune checkpoint genes and AKI/67 than PCA

• Given their rarity, characterisation of these tumours has been limited.

Primary aim: perform the first comprehensive multi-omic molecular, morphological and clinical characterisation of supra-carcinoids

Methods for identification of supra-carcinoids

• Established a new cohort of 91 PCA with clinical and morphological data, as well as whole-genome sequencing (WGS), RNA sequencing, and DNA methylation array data.

• Identify potential instances of supra-carcinoids by examining molecular clusters and tumour histology
  - Principal components analysis and consensus clustering of gene expression and methylation data from PCA and LCNEC (addition of published datasets) identiﬁes PCA with LCNEC-like molecular features.
  - Analysis of tumour histology: mitoses, necrosis, Ki-67, and protein expression of immune checkpoint genes identifies PCA with LCNEC-like histology

• 11 new potential supra-carcinoids were identiﬁed in addition to the six previously described based on their gene expression and/or DNA methylation proﬁle

• These patients had signiﬁcantly poorer survival than typical carcinoids, and no difference in survival was observed between supra-carcinoids and LCNEC.

Next steps towards molecular, clinical and morphological characterisation of pulmonary supra-carcinoids

• Compare the results of molecular clustering data with histological analyses (including NanoString DSP analysis of immune checkpoint genes), to conﬁrm supra-carcinoid cohort

• Integrate WGS data (copy number variants, small and structural variants) with gene expression and DNA methylation data using Multi-Omics Factor Analysis to characterise the molecular proﬁle of supra-carcinoids

• Correlate the molecular proﬁles with clinical and morphological features

References
5. Laddha SV et al Cancer Research, 2019 PMID: 31304744

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