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Canine idiopathic pulmonary fibrosis and lung cancer: common cellular markers and promising perspectives

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Canine idiopathic pulmonary fibrosis (CIPF) is a progressive and fatal interstitial lung disease that predominantly affects senior West Highland white terriers (WHWT). In humans, patients suffering from idiopathic pulmonary fibrosis have an increased risk of lung cancer, which worsens prognosis and suggests that fibrosis and carcinogenesis are interconnected pathological processes. In the general canine population, primary lung cancer is relatively rare but carries a poor prognosis in advanced stages. Besides, dogs affected by pulmonary fibrosis might be prone to developing lung cancer. This project aimed to enhance understanding of the pathogenesis of both diseases by exploring the molecular alterations in lung cells in CIPF and canine pulmonary adenocarcinoma (PAC), and to develop a tool for assessing the expression of novel disease biomarkers in vivo.
Single-cell RNA sequencing was performed on fresh post-mortem lung biopsies from four dogs free of lung disease and euthanised for unrelated reasons to generate a comprehensive cell atlas of the healthy canine lung. Forty-six lung cell subtypes were identified, along with cell type-specific gene expression profiles. This reference was used to identify disease-associated cell types and gene expression alterations in three primary PAC samples, obtained after curative lobectomy, and in two CIPF post-mortem lung biopsies. In PAC, tumour-associated macrophages overexpressed osteopontin (*SPP1*), while cancer-associated fibroblasts overexpressed genes involved in contractility, inflammation, and matrix remodelling, such as collagen triple helix repeat containing 1 (*CTHRC1*) and fibroblast activation protein (*FAP*). In CIPF, macrophages and fibroblasts also overexpressed *SPP1* and *FAP*, respectively. FAP expression was further investigated by immunohistochemistry in post-mortem lung biopsies from 22 WHWT affected by CIPF and 15 dogs free of lung disease, as well as in 6 PAC biopsies. FAP expression was observed in fibroblasts within areas of active immature fibrosis in CIPF and in cancer-associated fibroblasts in PAC but was absent from healthy lung tissue. Finally, in an experimental pilot study, positron emission tomography using a fluorine-18 labelled FAP inhibitor [^{18}F]FAPI-74 (SOFIE, iTheranostics, Dulles) was performed on two healthy senior Beagle dogs and two WHWT affected by CIPF and revealed a marked uptake in CIPF-affected lungs and no uptake in healthy lungs.
In conclusion, this project identified common disease-associated cell states and markers in CIPF and PAC, including SPP1^{+} macrophages and FAP^{+} fibroblasts. Furthermore, FAP-targeted in vivo imaging appears promising for the diagnosis and follow-up of CIPF and, most likely, canine lung cancers.

Disclosures
SOFIE (iTheranostics) graciously provided [18F]FAPI-74 but was not involved in the study design, collection, analysis and interpretation of data.

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